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PATHS OF PROGRESS OF OPHTHALMOLOGY

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BALTIMORE

> Let thine eyes look right on, and
> let thine eyelids look straight before
> thee.
> Ponder the path of thy feet, and
> let all thy ways be established.
>
> Proverbs IV: 25 and 26.

The story of medicine from its beginnings to the present state of knowledge is a romance of great incidents, an unfolding plot of surprise and wonderment. From out of this vast subject it is not without profit to choose a single chapter: the paths of progress of modern ophthalmology.

It is my purpose to follow in the steps of the pathfinders from their early discoveries in unknown regions, which have led to that splendid and beneficent attainment of knowledge and practice which ophthalmologists are privileged to study, to serve, to extend and to enjoy.

I shall begin the journey at the end of the Middle Ages. It is known that the state of medicine then was one of complete sterility. In the words of Osler [1]: "Following the glory that was Greece and the grandeur that was Rome, a desolation came upon the civilized world, in which the light of learning burned low, flickering almost to extinction." Allbutt [2] ascribed the extreme degeneration of surgery during the Middle Ages to the complete divorce of surgery and medicine, which in Greece had been wholly one. Their reciprocal benefits had been lost.

The Arab world had salvaged some of the ancient learning and had produced a voluminous literature, but nothing had entered Europe through the complete embargo which lasted until the end of the eleventh century. It was not until the thirteenth century that "the Arabist

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1. Osler, W.: The Evolution of Modern Medicine, New Haven, Conn., Yale University Press, 1921.

2. Allbutt, T. C.: The Historical Relations of Medicine and Surgery to the End of the Sixteenth Century, London, Macmillan & Co., 1905.

culture was grafted upon European medicine," and it was the pre-Renaissance period in which this culture became dominant.[3] It was the Byzantine and Arabian medicine which is embraced under the term Galenic medicine. Again to quote Osler:[1]

> There was indeed every reason why men should have been content with the physiology and pathology of that day, as, from a theoretical standpoint, it was excellent. The doctrine of the four humors and of the natural, animal and vital spirits afforded a ready explanation for the symptoms of all diseases and the practice of the day was admirably adapted to the theories.

The system was harmonious and was accepted as the perfection of knowledge and wisdom. Thus it naturally gained the position and the power of an authority which it was well to study and to enlarge by commentary—but not to question or to doubt.

The sanctity of this authority was but little less than was that held by Ptolemy's system of the heavens.

Surgery had fallen to the lowest level during the Middle Ages; it was in the hands of lowly and unlettered men. It is at this level that ophthalmic medicine and surgery are found at the end of the Middle Ages.

Hirschberg[4] pointed out that in the half millenium from the ninth to the fourteenth century the Arabians produced some sixty works on ophthalmology, while during this period in Europe there were but two of note, that of Zacharias and that of Benevenutus Grapheus (Grassus).

There is no better index of the state of ophthalmic practice in European lands during the Middle Ages than is found in the work of Grapheus, "De oculis."[5] According to Casey Wood, who made an admirable translation of this work, Grapheus was born not later than the tenth century. Other authorities hold to much later dates. Grapheus wrote:

> Let those of my hearers who wish to learn all the details of a new science, and to acquire fame thereby, listen to a discourse by an expert on the eye, composed by me, Benevenutus, and based on the teachings of the ancients as well as on my own wide experience gained by practice in various parts of the world. I have visited, for the purpose of my art, both hot and cold countries, and with divine help have cured many infirmities and operated on numerous cases of disease affecting all parts of the eye. Many of these ocular affections are quite unknown, even their proper names being new to medical men. Nevertheless it is my intention in every instance to publish the plain truth about all diseases of the eye and to declare especially what

3. Garrison, F. H.: Introduction to the History of Medicine, Philadelphia, W. B. Saunders Company, 1929.

4. Hirschberg, J.: Geschichte der Augenheilkunde in Graefe, A., and Saemisch, E. T.: Handbuch der Gesamten Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1915, vol. 13, p. 90.

5. Grassus, B.: De oculis: Eorumque egritudinibus et curis, translated with Notes and Illustrations from the First Printed Edition, Ferrara, 1474 A. D., by C. A. Wood, Stanford University, Calif., Stanford University Press, 1929.

disorders may be cured by powders, collyria, plasters, ointments, pills, purgation by electuaries and by treatment with the cautery, as well as to speak of the diet, restriction of the regimen, and other precautions by which one may guard against over-indulgence in rich and improper food.

There follow fifty short chapters. Two are on the structure of the eye. Eight are on the varieties of cataract, which disease Grapheus divided into seven kinds, four curable and three incurable (first, gutta serena, with a clear large pupil; second, the cataract which arises suddenly and in which the pupil is greenish, and, third, the cataract accompanied with such enlargement of the pupil that the iris cannot be seen). The sixth chapter is devoted to operations for cataract. One chapter is on other diseases or accidents, e. g. pruritus palpebrarum. Two are on ophthalmia and seven on panniculus, which Wood interpreted as granular or follicular conjunctivitis. These are followed by chapters on disease due to excess of phlegm and to ingrowing eyelashes. The rest of the work deals with dimness of sight, with muscae volitantes.

One looks for conditions which can be recognized clinically in the chapter on ophthalmia; this term, however, appears to embrace all acute congestive ocular conditions from acute conjunctivitis to panophthalmitis, for one finds a condition "most frequently between the end of August and the last of September" and another in which "the ocular humors are destroyed by severe pain . . . the contents of the eye runs out between the eyelids and . . . [the disease] is followed by total loss of vision." Hirschberg called special attention to Grapheus' reference to trachoma and its mechanical treatment (Grassus,[5] chapter 28):

> In this affection the eyes appear swollen and are continually tearing. . . . When you wish to be sure of the sort of infirmity you are dealing with, invert the upper lid with your fingers, when you will observe that the internal lining is thickened with granular deposits, with substance like grains of millet. . . . After preliminary treatment evert the diseased lid and squeeze out the fleshy growths with the fingers aided by the knife. . . . Among Saracen women it is the custom to . . . rub the diseased surface vigorously with a fig leaf until the blood comes. This treatment gives temporary relief, as does the same method with sugar; but in both instances the disease recurs.

There is the statement of a noted professor of medicine in Padua, Benedetti, who lived in the latter part of the fifteenth and the early part of the sixteenth century, that (in Italy) the "diseases of the eye, which are almost without number and which should demand care of oculist-physicians . . . are relegated to the care of the ignorant laborers and rustics." He said also: "In Greece oculists, as well as surgeons, are wanting . . . But in Asia, namely in Syria and in Media, excellent oculist-physicians are to be found." (Hirsch,[6] page 295.)

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6. Hirsch, A.: Geschichte der Ophthalmologie in Graefe, A., and Saemisch, E. T.: Handbuch der Gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1877, vol. 7, pt. 1, pp. 235-554.

Medicine was in a static condition, in a maze; practitioners were treading narrow tortuous paths that led them around but advanced them no farther.

But there came a great awakening—the Renaissance. What was the magic wand that brought about a revolution in all the natural sciences? It was "doubt." Men began to question the authority of traditional views and systems. They came to realize that scientific progress demanded—not scholastic rationalizing—but observation and experiment, and rigorous proof. The fifteenth century was the true dawn that brightened more and more unto the perfect day . . . Medicine joined heartily, though slowly, in the revolt against medievalism. (Osler,[1] page 126.) Two great physicians appeared on the scene: Copernicus wrote his great work in 1530 and saw it published in 1543 when he lay on his death bed; in the same year Vesalius' "Fabrica" saw the light of day. These two events alone qualify the sixteenth century for its great distinction!

Since 1543 a vast continent of medical science has been opened.

How has the progress of ophthalmology been attained, how were its problems met, how were they solved? In the long quest of discovery, what was the measure of indebtedness of each investigator to the labors of those that had gone before in the same scientific paths or in others far removed? My chief purpose now is to show the ways which the pathfinders opened.

Vesalius (1514-1564) was the pioneer in the realm of modern medicine. His "Fabrica" [7] is "the *chef d'œuvre* of any medical library." (Osler,[1] page 154.) He was the pathfinder in renascent ophthalmology. This statement will surprise some persons who remember how few of his descriptions concerning the anatomy of the eye were in advance of what the ancients had known and that he included some traditional errors, such as placing the crystalline lens in the center of the eyeball and the entrance of the optic nerve on the temporal side and describing a retractor bulbi muscle in the human being. Side by side with his admirable illustrations of dissections one finds his illustration of the eyeball but little better than that of the Arabians. But it is not astonishing that Vesalius at the age of 28 was not able to complete the entire labor which vast numbers of anatomists have striven to accomplish during the centuries. It is interesting that his investigations did include the eye. Vesalius found that the anterior chamber was filled with a liquid humor, watery and not "like the white of egg," as was thought. It was Vesalius who described the crystalline humor (lens) as "most pellucid and as of double convexity; when taken out of the eye it magnifies, like a magnifying glass, objects upon which it is placed, as

7. Vesalius, A.: De humani corporis fabrica libri septem, Basel, ex. off. J. Oporini, 1543.

certain mirrors do." And then he added, "I cannot mention here or discuss in detail that the crystalline humor is the main instrument of vision . . . as Galen describes, since I do not know how vision comes about." The great biographer of Vesalius, Roth,[8] concluded that Vesalius "understood that the traditional theory of vision was not satisfactory; but having no new one to replace it he passed over the matter without further discussion." However, in describing the optic nerve he noted that the retina was regarded by some investigators as the chief organ of vision.

I have mentioned these observations, interesting as they are, for the purpose of showing that it is not because of them that Vesalius must be looked on as the pioneer in ophthalmology. Urged by the real scientific spirit, by that curiosity which expresses itself in the search for truth, he studied the classic works of Galen but did not accept their statements as truth unless study of the body confirmed them. For him there was no authority but nature, and her answer was given to him who searched her with earnest and painstaking study. Vesalius returned to the art of Hippocrates, the art of observation, of accurate search, and applied it to human anatomy. Vesalius had the self confidence to rely on his careful observations, and he had the courage to affirm and demonstrate and teach them and to deny statements contrary to what he had convinced himself was the truth.

But the power of Galenic thralldom was such

> that even at the most liberal University of Padua, Vesalius, for a long time, did not dare to teach what he really saw, but accommodated his statements to the accepted dogmas of Galen. When he finally allowed himself to state the facts, and even offered to prove his statements publicly . . . the opposition was so persistent that in a fit of passion he tore up his manuscripts and left the university for the Court of Spain. (Ornstein.[9])

His great service was that of a master builder who taught his disciples, who taught their disciples throughout the generations, the art of studying the structure of the organs and their functions by reliance solely on closest observation. The proof followed in the steady growth with ever increasing momentum of knowledge of the anatomy of the eye. Vesalius had cast off the shackles of authority and had opened a new path in medicine. To quote Foster:[10]

> He taught in such a way that his disciples, even when they thought him greater than Galen, never made a second Galen of him; they recognized that they were most truly following his teaching as a whole, when they appealed to observation to show

8. Roth, M.: Andreas Vesalius Bruxellensis, Basel, B. Schwabe, 1886, p. 153.

9. Ornstein, M.: The Role of Scientific Societies in the Seventeenth Century, ed. 2, Chicago, University of Chicago Press, 1928.

10. Foster, M.: Lectures on the History of Physiology During the Sixteenth, Seventeenth and Eighteenth Centuries, New York, The Macmillan Company, 1924, pp. 10-11.

that in this or that particular, his teaching was wrong. After him back-sliding became impossible.

The names of many anatomists who followed Vesalius and who built up knowledge of the structure of the eye are familiar: Fallopius (1523-1562), Meibom (1638-1700) and Briggs (1641-1704), within the next one hundred years; then Fabricius ab Aquapendente (1537-1619), who first used frozen eyes for sectioning to find the correct position of the lens; Scheiner (1575-1650), whose studies were made on mammalian eyes, and Huygens (1629-1695); Leeuwenhoek (1632-1723), who made the first investigations with a microscope, toward the end of the seventeenth century. Petit (1664-1741), especially, and Huygens made accurate measurements of frozen sections of the various parts of the human eye and of the radius of curvature. Winslow (1669-1760), Albinus (1697-1770), Haller (1708-1777) and, especially, Zinn (1727-1759) made great contributions. The eighteenth century closed with the appearance of the marvelous work of Soemmerring (1755-1830). It is needless to mention the monumental works on the anatomy of the eye published in the nineteenth century. (Henle's [11] description of 1866 covers one hundred and forty pages.) One can see the progress that was made in the illustrations which accompanied the publications. A few only can be shown in the accompanying photographic copies (figs. 1 to 15).

PHYSIOLOGY OF VISION

Foster [10] stated that "in a sense Vesalius was the author of discoveries [in physiology] which were made after him." The first pioneers in physiology were two great scientists, Kepler and Harvey. The former, an astronomer, opened a second path of ophthalmic study and discovered the physiology of vision half a century after Vesalius' work first appeared.

"Plato supposed, that, both from the Eye and the Object, there came substantial Effluvia, which, meeting with one another Midway, embraced one another, then returned, and made their Report to the Eye, and so to the Mind, for causing the Sense of Seeing." (Porterfield,[12] page 351.) Thus may have arisen "The eyes shot forth bolts," etc.

The great Arabian scholar Alhazen (Abu ali al-Hazen ibn al Haitham, 965-1038), "the greatest Muslim physicist and one of the greatest students of optics of all times, also astronomer, mathematician, physician" (Sarton [13]), in his important work on optics had denied the

11. Henle, F. J. C.: Handbuch der systematischen Anatomie des Menschen, Brunswick, F. Vieweg u. Sohn, 1866, vol. 2.

12. Porterfield, W.: A Treatise on the Eye: The Manner and Phaenomena of Vision, Edinburgh, G. Hamilton & Balfour, 1759, vols. 1-2.

13. Sarton, G.: Introduction to the History of Science, Baltimore, Williams & Wilkins Company, 1927, vol. 1, p. 721.

validity of the Greek theory and had taught that the visual rays were sent out from the illumined object to the eye. A significant and weighty statement of Alhazen was cited by Hirschberg [4] (volume 13, page 161): "All vision is brought about by refraction. And moreover, whatever is known about vision must be understood as refraction, a fact never expressed by any of the ancients." Alhazen's work was translated into Latin in the thirteenth century by Vitellio and enjoyed such

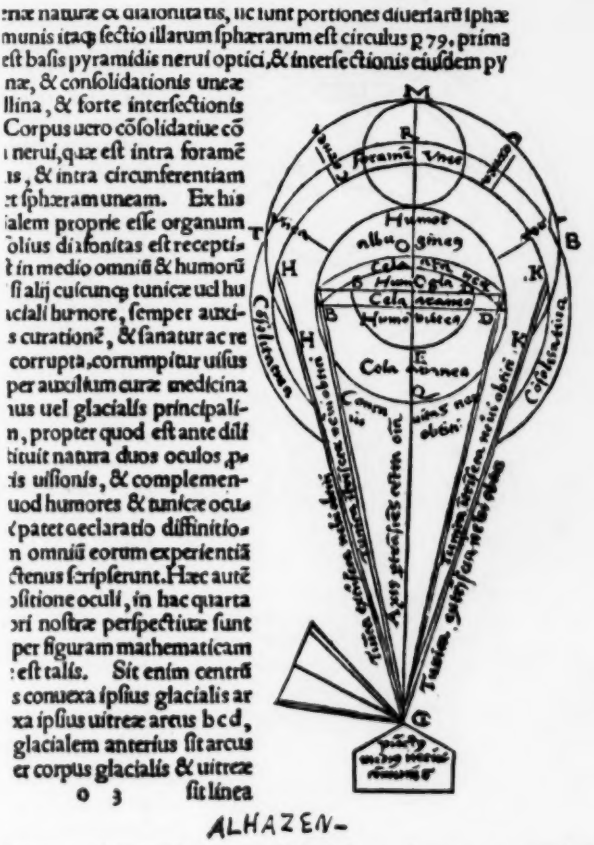

næ naturæ & diaphanitatis, hæ sunt portiones diuersarū sphæ
munis itaq; sectio illarum sphærarum est circulus p 79. prima
est basis pyramidis nerui optici, & intersectionis eiusdem py
næ, & consolidationis uneæ
llina, & forte intersectionis
Corpus uero cōsolidatiue cō
i nerui, quæ est intra foramē
is, & intra circumferentiam
t sphæram uneam. Ex his
ialem proprie esse organum
olius diaphonitas est recepti-
t in medio omniū & humorū
si alij cuiuscunq; tunicæ uel hu
ciali humore, semper auxi-
s curationē, & sanatur ac re
corrupta, corrumpitur uisus
per auxilium curæ medicina
ius uel glacialis principali-
n, propter quod est ante dis
tituit natura duos oculos, p
is uisionis, & complemen-
uod humores & tunicæ ocu
patet declaratio diffinitio-
n omniū eorum experientiā
ctenus scripserunt. Hæc autē
ositione oculi, in hac quarta
ori nostræ perspectiuæ sunt
per figuram mathematicam
: est talis. Sit enim centrū
s conuexa ipsius glacialis ar
xa ipsius uitreæ arcus bcd,
glacialem anterius sit arcus
er corpus glacialis & uitreæ
o 3 sit línea
ALHAZEN-

Fig. 1.—Alhazen (965-1038): Vitellio's thirteenth century translation (Basel, 1535), page 55.

esteem that Kepler in 1604 gave his own work the title "Supplement to Vitellio" ("Ad Vitellionem paralipomena"), a modest title indeed for one of the greatest contributions to science, a work which presented a new theory of the physiology of vision, the theory which essentially is that accepted today.

Before Kepler, Felix Plater (1536-1614), professor of medicine in Basel, had enlarged on the observation of Vesalius; he stated that the

crystalline humor is a lens (perspicillum) and forms images of external objects on the retina and that these images are magnified. Thus, in 1583, he regarded the retina as the chief factor of vision. (Hirschberg,[4] volume 13, page 295.)

Maurolycus (1494-1577), a priest and teacher of mathematics in Messina, had earlier but less definitely suggested that an image (reduced

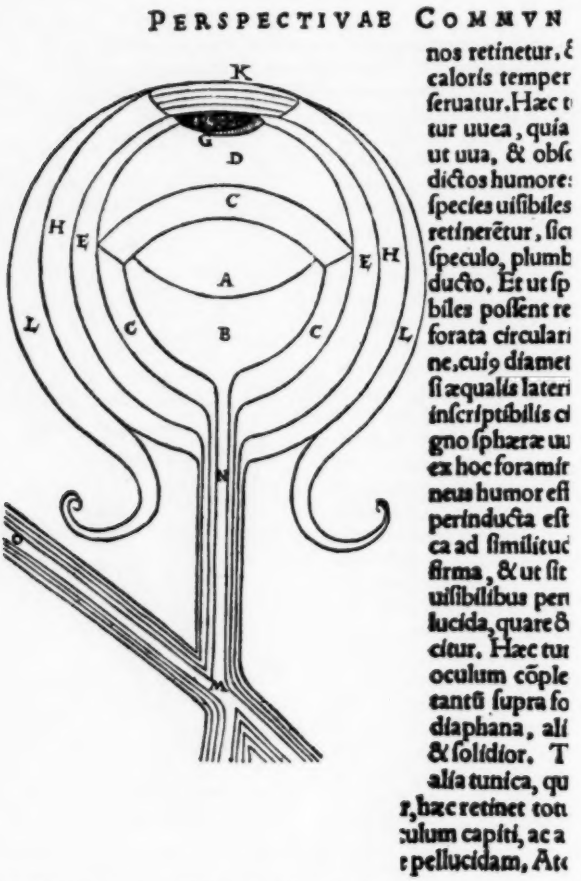


Fig. 2.—Peckham (-1292), archbishop of Canterbury from 1279 to 1292: "Perspectiva communes" (Nuremberg, 1542), propositio XXX.

but not inverted) is formed on the retina. (Hirschberg,[4] volume 13, page 294.)

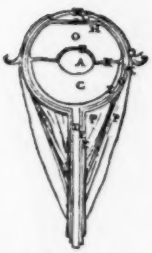
And della Porta (1538-1615), of Naples, had performed the interesting experiment of allowing light to pass into a darkened room through a small opening to produce images on a white surface opposite. He had even placed a convex lens before the opening and thus obtained a sharper image and had used the principles involved in constructing the camera

obscura. He noted the effect of light in contracting the pupils and that the crystalline lens is placed near the pupil. Della Porta applied the facts he had observed to the eye; the rays of light passed into the eye as they did through the small opening into the room. But he still clung to the ancient Greek view that the image was formed in the lens!

It was Kepler (1571-1631) who followed Plater and della Porta and who solved the optical problems. He and the investigators who followed him showed their dependence on the discoveries in the anatomy of the eyeball. Their paths kept in close touch with that of the anatomists!

DE OCVLO VISVS INSTRVMENTO.
Caput XIIII.

PRIMA DECIMIQVARTI CAPITIS
FIGVRA.



HAEC figura earum quæ præsenti Capiti præponuntur prima, alteram oculi partem exprimit, una sectione ab anteriori sede per posteriorem, atq; ita per neruum uisorium diuisi: perinde scilicet, ac si quis diuisæ secundùm longitudinem cepæ alteram partem ea superficie delinearet, qua alteri parti connata continuaq; fuerat. Atq; hoc quoq; modo cœlos, & quatuor elementa in plano depingere solemus.

A Humor crystallinus.
B Tunica anteriori humoris crystallini sedi obducta, & tenuissimæ ceparum pelliculæ instar pellucida.
C Humor ultreus.
D Nerui uisorij substantiã.
E Tunica quam reti assimilamus, quamq; resoluta uisorij nerui efficit substantia.
F Tenuis cerebri membranæ portio, neruo uisorio obducta.
G Vuea tunica, in quam tenuis uisorium neruum induens membrana degenerat.
H Hac sede uuea tunica in posteriora cõprimit, neq; corneã extertùs illi obductã cõtingit tunicã.
I Forumen, quo uuea foratur, ipsa'ue pupilla.
K Tunica ab uuea initium ducens, & ciliis seu palpebrarum pilis imagine correspondens, ac interstitium pariter utreti humoris ab aqueo.

Hh 4 L Duræ

Fig. 3.—Vesalius (1514-1564): "Fabrica" (Basel, 1543), page 643.

Let me quote one of Kepler's most distinguished followers, Porterfield, who wrote about his work a century and a half later (Porterfield,[12] volume 1, pages 360-361):

The learned Kepler made the grand discovery, and showed, by his geometry, in what manner the rays were refracted thru' all the Humours of the Eye, and formed a distinct picture upon the Retina. . . . He also discovered the Constitution of defective eyes, that is, how the Pictures became confused, and showed in what Manner they are rendered distinct by Spectacles, and concave Glasses, whose Effects have been most admired from the Time of their Invention . . . and had long perplexed the greatest wits to account for them. The Vulgar Account of Objects

appearing erect, notwithstanding the Invertion of the Pictures upon Retina is also Kepler's, who tells us that the Mind perceiving an Impulse of the Ray on the lower Part of the Retina, considers this Ray as directed from the higher Part of the Object.

Kepler discovered that the center of the retina has the most acute vision, and he described the difference in the convexity of the lenticular surfaces, as also the function of the uveal tract of preventing light from

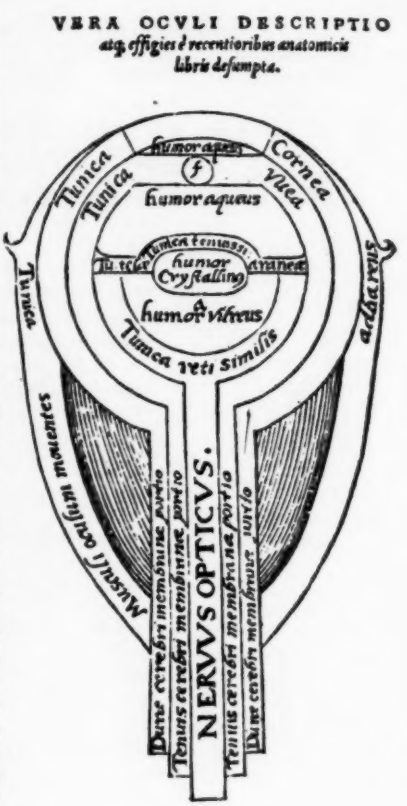


Fig. 4.—Alhazen: Vitellio's Latin translation (Basel, 1572), page 87.

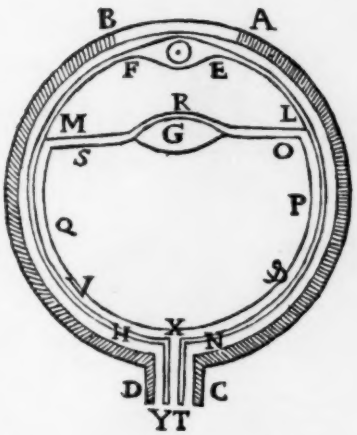
passing through the coats of the eye. Kepler was, therefore, the pioneer in discovering the physics of vision.

Kepler himself recognized that he was a pioneer. In the introduction of his "Mathematici Dioptrice" (1611) he wrote: "Since I published six years ago the optical part of astronomy in which I described a new conception of the mechanism of vision and the action of glasses, to my

knowledge as the very first, these facts have until now remained unshaken." (Hirschberg.[4])

Spectacles with convex glasses, it may be remembered, were invented at the end of the thirteenth century and those with concave glasses a century later. Physicians have left no signs of special interest in them. Della Porta, who was not a physician, recognized their value, declaring in 1593 that "deprived of spectacles we should be almost as orphans in

ſphæras viſui obiectant, vt vnico intuitu totius fabrica contempletur.



A B C D dura tunica, cuius pars A B inſtar cornu pellucet & degenerat in craſſam meningem C D.
E F N H vuea, cuius pars I, feneſtrata pupilla eſt, & degenerat in tenuem meningem T Y.
O R S aranea tunica.
& V X retiformis.
L R M humor aqueus.
G humor cryſtallinus.
P Q humor vitreus.
C D neruus opticus.

Fig. 5.—Baptista della Porta (1538-1615): "De refractione" (Naples, 1593), page 68.

vision." (Hirschberg.[4]) It remained for Kepler, the mathematician, to explain their action!

Kepler was soon followed by Scheiner,[14] a Jesuit teacher of mathematics, who, in his "Oculus, hoc est fundamentum opticum," published in 1619 (a second edition in 1652), gave proof of the correctness of Kepler's description; by exposing a portion of the sclera at the posterior pole of an enucleated eyeball he demonstrated the inverted image on

14. Scheiner, C.: Oculus, hoc est fundamentum opticum, Oeniponti, apud D. Agricolam, 1619.

the retina (Rome, 1625). He devoted a chapter to proving that "vision is produced in the retina but not in the crystalline humor." Ophthalmologists are all familiar with Scheiner's experiment "of looking through a card with two small holes, closely placed." Scheiner suggested using glass balls of different diameters placed near the eye, watching the size of the reflected images and comparing them with the same images in the cornea to measure the corneal curvature. This idea was later used for ophthalmometry.

Plempius [15] was a poor prophet when he wrote (1632): "Kepler has explained the theory of vision so perfectly that he has not only far

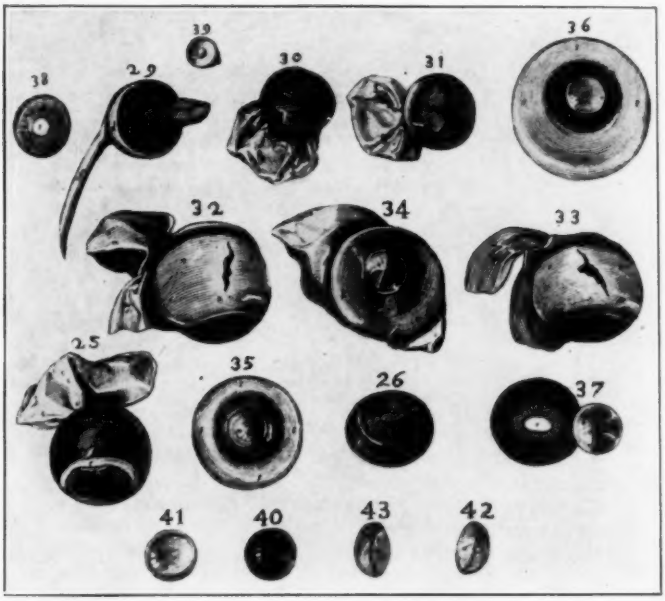


Fig. 6.—Fabricius ab Aquapendente (1537-1619): "De visione" (Venice, 1600), page 35.

excelled all his predecessors but that he has made it impossible for any who follow him to add to its accuracy."

Descartes (1636) supposes Vision is performed by bare Motion only, without any material emanation from the object; but only that the Light (which with him . . . is but the Motion of the finer Parts of the Medium) moves the Eye just after the same Manner as the Object is supposed to have determined it, which Motion is continued along the Optic Nerve up into the Brain, where it moves the Conarium, or Glandula Pinealis, with him the Seat of the Soul, and by that Means produces internal Sensation and enables the Soul to judge accordingly. (Porterfield,[12] page 351, see figure IX.)

15. Plempius, V. P.: Ophthalmographia, sive tractato de oculo, Louvain, sumpt. H. Nempœi, 1632.

An interesting summary of the several theories to account for accommodation is found in that splendid work of Porterfield [12] (1759) just quoted:

In order to see Objects at different Distances distinctly: It is necessary that there should be a Change in the Eye, lest the place which the Picture of the Object is

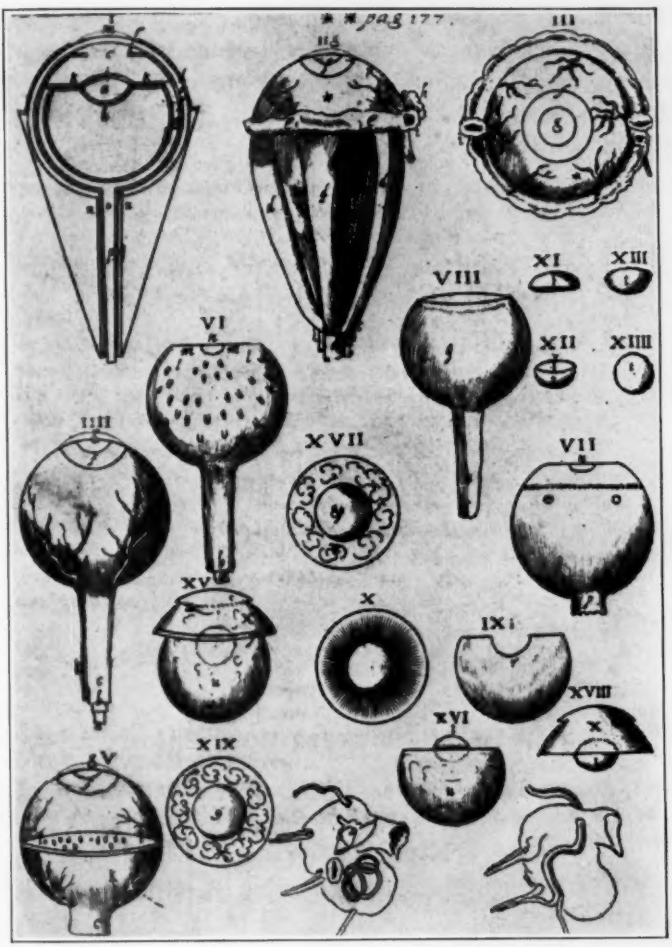


Fig. 7.—Kepler (1571-1631): "Ad Vitellionem" (Frankfort, 1604), page 176. Almost all these drawings were taken directly from Vesalius.

exact should fall short of or beyond the Retina. . . . Most Physicians, as well as Philosophers, have been brought to believe that we have a Faculty of changing the Conformation of our Eyes . . .; Mr. de la Hire is of a contrary Opinion and contends that . . . the Eyes never alter their conformation; [and this he demonstrates by experiment and] that from an anatomical examination, of all parts belonging to our eyes, it will be found that none . . . are capable of making any

of those Changes . . . that are supposed necessary for seeing distinctly at different Distances.

Porterfield,[12] by many experiments, proved the fallacy of de la Hire's view and likewise of the more generally accepted opinion that a change in the length of the eyeball could be affected by the ocular muscles (volume 1, pages 437 and 446). He favored the view "that the Ligamentum Ciliare is excellently qualified for changing the Situation of the Crystalline and removing it to a greater distance from the Retina, when Objects are too near us . . . it will also compress the Vitreous Humours" and thus "push it [the crystalline lens] forwards."

He described the theory that

the Ligamentum Ciliare . . . does by its Contraction draw the edge of the Crystalline . . . and by that means makes it broader and flatter than before

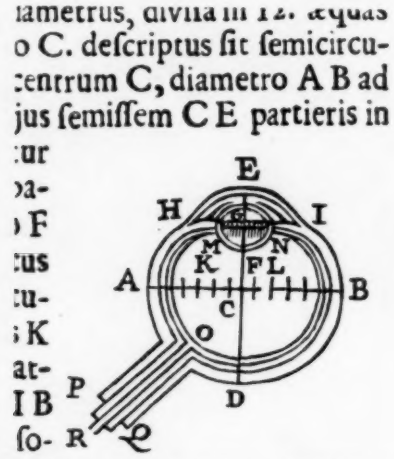


Fig. 8.—Scheiner (1575-1650): "Oculus" (second edition, London, 1652), page 17.

when objects are at a distance from the Eye; and that when we view nearer objects this Ligament is relaxed and the Crystalline recovers its convexity by the Elasticity of its Parts.

Porterfield rejected this theory, contending that the direction of the pull makes the assumption impossible, and he based this conclusion on an anatomic drawing (which is erroneous) as well as on other objections.

It was Descartes who, in 1637, first proposed the theory later supported by Thomas Young; the latter proved by difficult experiments on his own eyes that accommodation is due to changes in form of the lens without lengthening of the eyeball.

I have indicated briefly the steps in the study of accommodation in order to point out the difficulty which earnest investigators found in solving the problem. Indeed the final proof was not established until half a century later, at the stage dominated by the physiologists Helm-

holtz and Donders, whose contributions raised physiologic optics to a high place among the sciences.

Mariotte, a French physicist in 1666 discovered the blindspot which bears his name. He made careful anatomic studies and noted the naso-lateral insertion of the optic nerve; he then studied the corresponding part of the field of vision and discovery of the blindspot followed. It is curious that he concluded that it was the choroid which was sensitive to light, a view long shared by other investigators.

In the middle of the seventeenth century the two great and fundamental theories of light, Newton's theory of emanation and Huygens' undulation theory, appeared, and after two and one-half centuries they

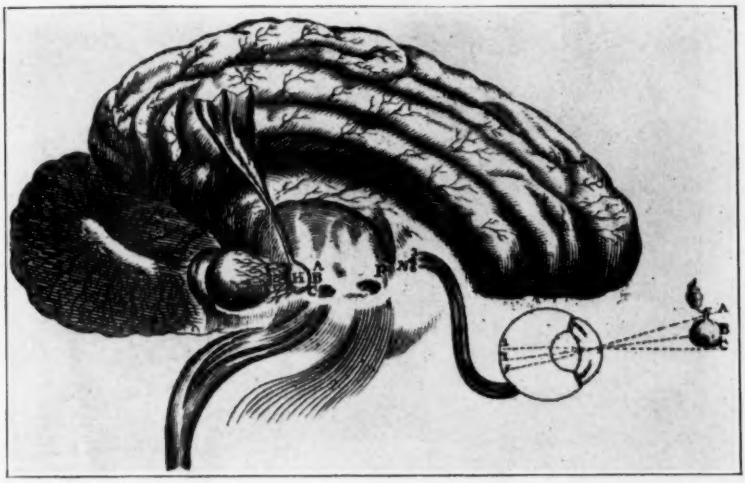


Fig. 9.—Descartes (1596-1650): "De homine" (Leyden, 1664), page 100. Descartes supposed that vision was performed by light which was bare motion only and that this motion moved the eye and was continued along the optic nerve up into the brain, where it moved the pineal gland, "the Seat of the Soul," and enabled "the Soul to judge accordingly."

have not found a final solution. (Hirschberg,[4] volume 14, part 1, page 386.)

Early references are found bearing on the extent of the field of vision in various directions; hemianopia had been recognized even by the ancient Greeks; Mariotte had discovered the blindspot. Still, almost a century and a half passed before Young first measured the field of vision, in 1801, and Purkinje, in 1825, measured it both for form and for color.

The earliest accurate measurement of the lower limit of visual acuity was made by Hooke, a physicist, in 1674. The eye cannot distinguish two points separated by less than one minute (1′). In this sphere of

investigation, too, a long period passed before clinical use was made of the fact discovered. (Hirschberg,[4] volume 13, page 313.)

PATHOLOGIC ANATOMY

I have thus far followed two paths, that of the anatomy of the eye and that of the physiology of vision, and it is a striking fact that the first was blazed by general anatomists and the second by physicists and mathematicians. Physicians paid them little attention. I shall now

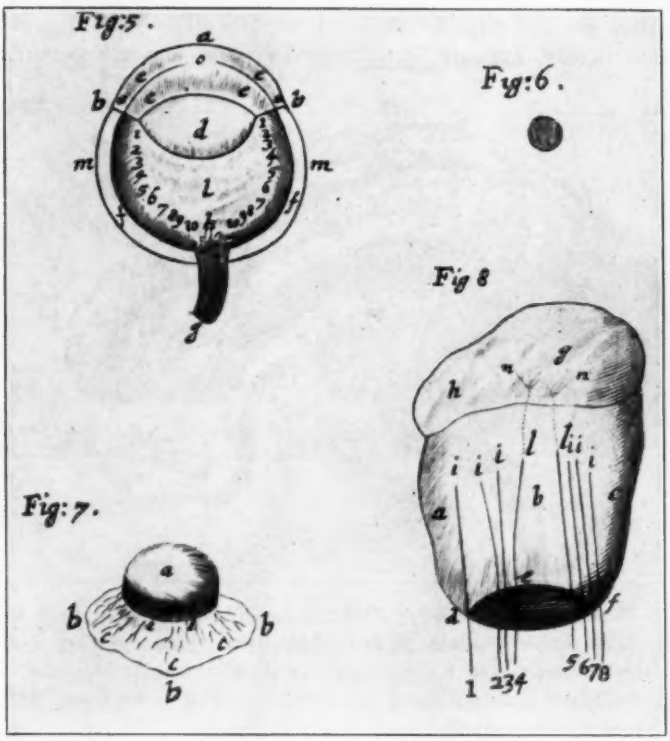


Fig. 10.—Briggs (1641-1704): "Ophthalmographia, Anatomy of the Eye" (London, 1685).

enter into a third path, that of the pathology of the eye. Kepler, pioneer in the physiology of vision, appeared half a century after Vesalius, but the pioneers in the pathology of the eye began making their observations more than two centuries after the great anatomist.

When Galenism thrived and all disease was regarded as disturbances of the humors, all diseases found easy explanation. There was, therefore, no essential reason for further investigation. Ignorance of normal conditions, furthermore, made their recognition difficult or impossible. The careful study of normal anatomy led to the observation of abnormal

conditions, and it was Vesalius himself who first made note of these. Thus, he recorded finding atrophy of the right optic nerve in a woman whose right eye had been blind and phthisical since childhood, and he noted the attenuation of the nerve up to the chiasm. Other scattered observations are met with in the writings of followers of Vesalius.

In 1679 Bonet[16] (1620-1689) published his "Sepulchretum, sive anatomia practica" (second edition, 1700). In this collection there are several cases of blindness due to tumor of the brain, cerebral hemorrhage,

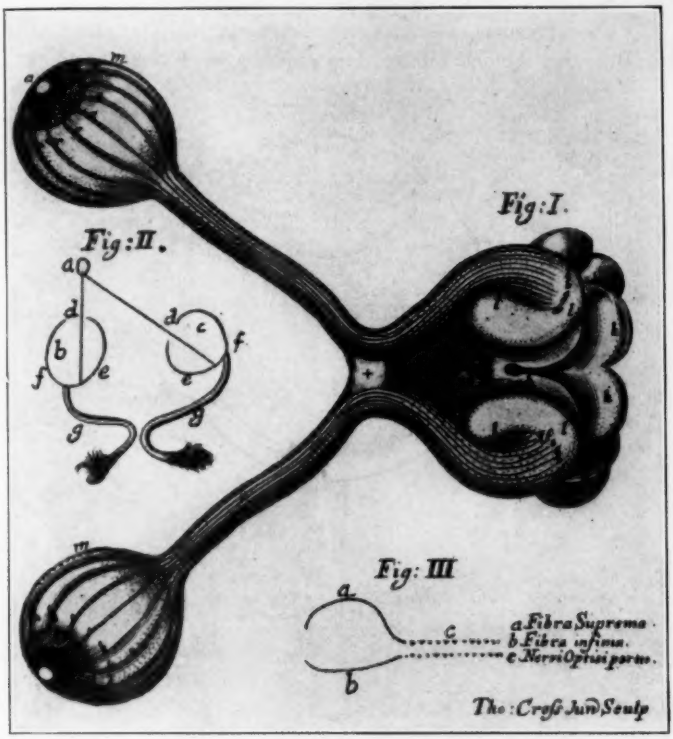


Fig. 11.—Briggs: "Ophthalmographia" (Cambridge, 1687). The chiasm was known to Galen and to the Arabians, who believed that the optic nerves met so that the central canals might be united. Vesalius described a case of nonunion, and Henle appeared to corroborate this finding.

abscess of the brain and hydrocephalus and 2 cases of ocular tumor. (Hirschberg,[4] volume 14, part 1, page 482.)

Far the most important early studies in the history of the pathologic anatomy of the eye led to the discovery of the seat of cataract in the crystalline lens. This discovery was not only conspicuously important

16. Bonet, T.: Sepulchretum, sive anatomia practica ex cadaveribus morbo denatis, Geneva, L. Chouét, 1679.

because it destroyed an age-long and almost imperishable fallacy, and because the demonstration was so convincing, but because it proved that fundamental pathologic facts can be solved by pathologic investigations and thus illumined the path of discovery.

The story is told in great detail by Brisseau in his several addresses before l'Academie Royale des Sciences and was republished in "Traité de la cataracte et du glaucome" in 1709.[17]

Sylvester O'Halloran,[18] in his "A New Treatise on the Glaucoma, or Cataract," gave the following account:

The first who attempted, with success, to shew the true seat of a cataract, were, Messieurs Brisseau, Antoine Maitre-Jan and Heister. Nor should we, on this

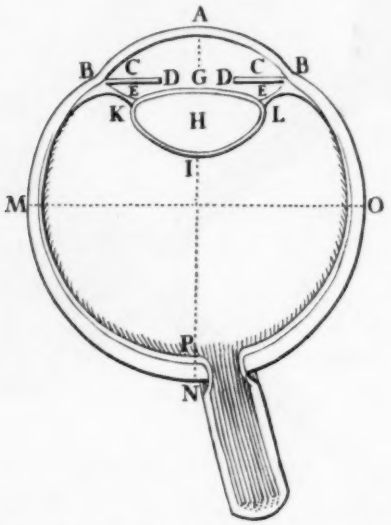


Fig. 12.—Petit (1664-1741), in *Mémoires de l'Academie Royale de la Chirurgie,* Feb. 11, 1725, page 20.

occasion, forget Petit the Physician, who has proved from Experience and the Structure of those Parts (the posterior Chamber of the Eye, being but ¼ of a line) the Impossibility of the Existence of a membranous Cataract there.

The first Observation was made by Brisseau, in 1705, on a Soldier, who laboured under a perfect Cataract. This Man, happening to die of a Flux, Brisseau depressed the Cataract, on the Body, with the some Precautions, as if on a living Subject, till such times as he saw the Opacity removed from behind the Pupilla. He then took out the Eye from it's Orbit, in order to examine the Body he had depressed. He therefore opened the Cornea, and after the Aqueous-humour's having discharged itself, he found, instead of a Membrane, the Crystalline-Lens itself opacous, and

17. Brisseau Jr.: Traité de la cataracte et du glaucome, Paris, Laurent d'Houry, 1709.

18. O'Halloran, S.: A New Treatise on the Glaucoma, or Cataract, Dublin, S. Powell, 1750.

depressed under the Vitreous-humour! To be more certain, he opened the other Eye, and found the Crystalline-Lens transparent, and in it's natural place.

This remarkable observation confirmed by very strong arguments, was read before the Royal Academy the Eighteenth of November, of the same year. But the

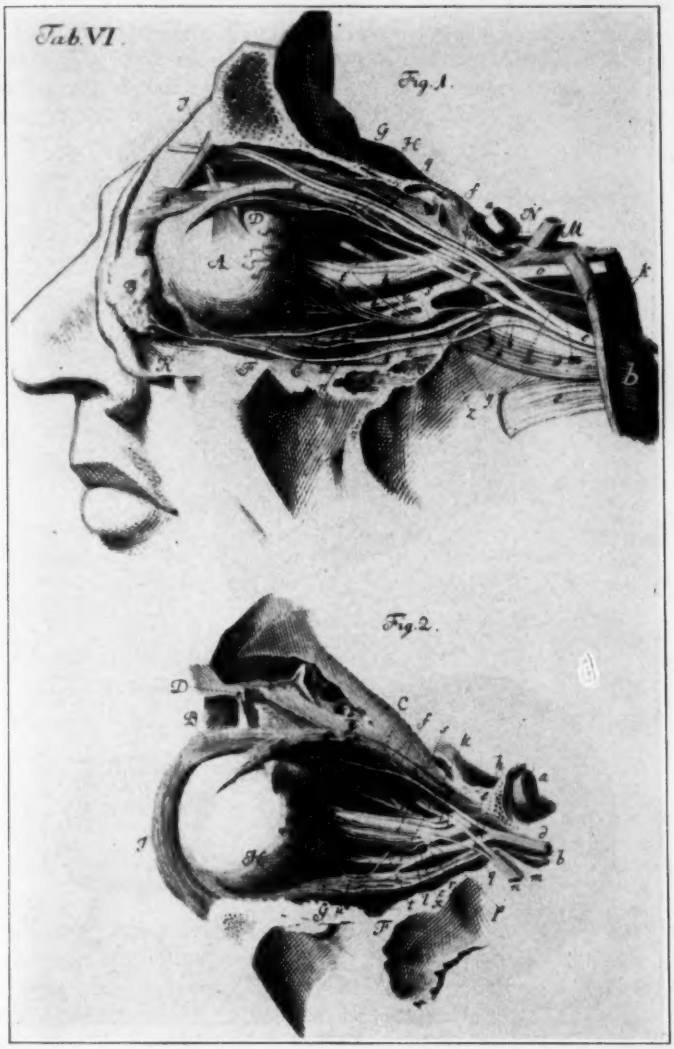


Fig. 13.—Zinn (1727-1759): "Descriptio anatomica oculi humani" (Göttingen, 1755).

Academicians seemed to make slight of this Discovery; nor did they think proper, to give it a Place in their Works. However this cool Reception did not deter Brisseau from maintaining his new Opinion, viz. That it was the Crystalline Lens, which was constantly obscured in the Cataract; and therefore,

In 1708, he published four cases more, to confirm his new Doctrine; in each of which he constantly found the Opacity, to be in the Crystalline Body itself, as in his first Experiment; and differing in nothing from it, except in the Degree of Colour and Consistence in this Body; as being sometimes harder, sometimes wider, or

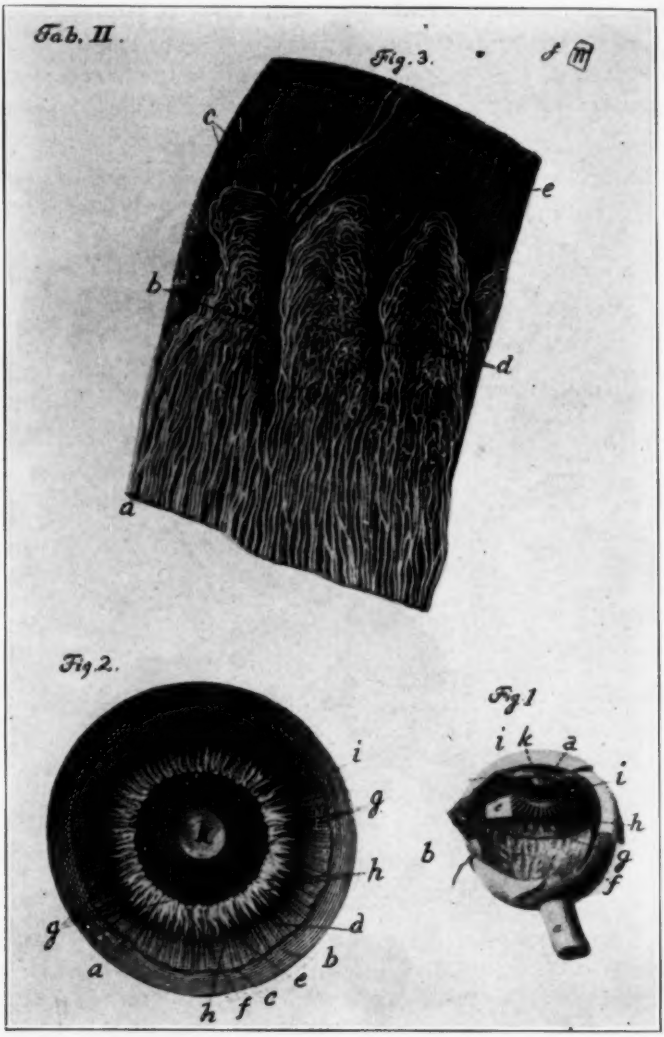


Fig. 14—Zinn: "Descriptio anatomica oculi humani" (Göttingen, 1755).

yellower; but never a Pellicle formed in the Aqueous-humour, as was before imagined.

In 1709, he collected all those pieces which he had separately published on this Affair; added to them several new Observations, both of his own and others; and, in a Word, seemed to make the true Seat of a Cataract indisputable. But as this was a great Innovation, with respect to the then received Opinion, of the Uses assigned

to the Crystalline-Lens; it did not fail of raising him a great many Enemies, both Physicians and Mathematicians; amongst whom, de la Hire the Father, Litré and Mery; and the noted English Oculist, Woodhouse, were his greatest Opponents.

Nor was Maitre-Jan wanting to confirm this new Doctrine by Facts. . . . You have two Histories: The first, of a person who died, labouring under a perfect Cataract; and on whom the Operation was not made. In examining this eye, he found the Crystalline-Lens in it's natural Place, but opaque; and as if infused in some acid Liquor. The other was of a Woman, on whom the Operation had been successfully performed, for both eyes. This Woman, dying some Time after, he examined both eyes; and found in each, the Crystalline-Lens opaque, and lying under the

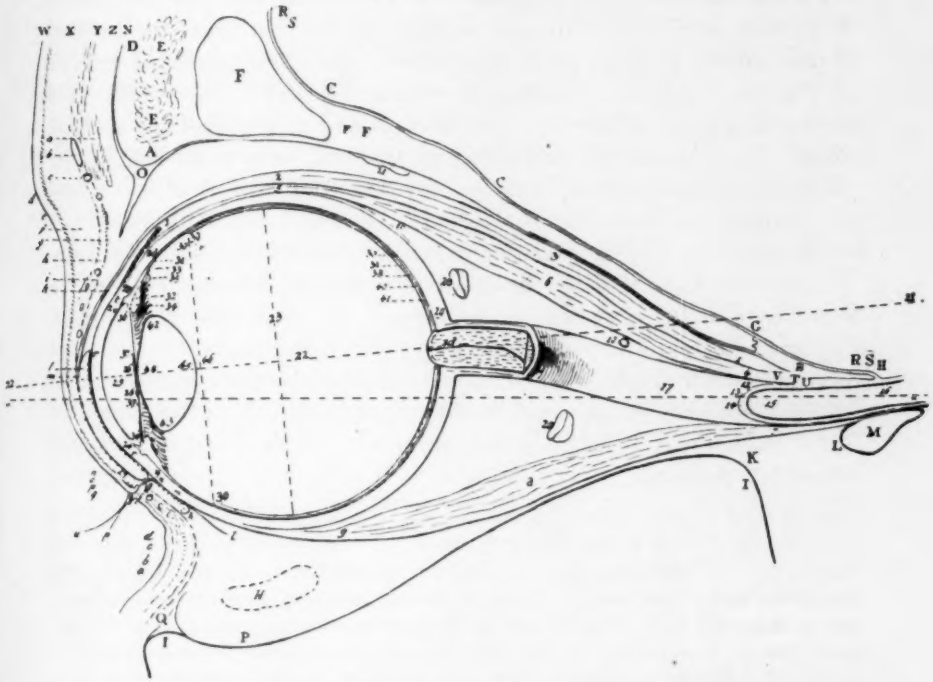


Fig. 15.—Soemmerring (1755-1830): "Icones oculi humani" (Frankfurt, 1801).

Vitreous-humour; and this last Convex in it's anterior Part, and occupying the Place of the depressed Crystalline.

However, it is to be noticed, that tho' Brisseau and Maitre-Jan were the first, who evidently demonstrated the Cataract, to be an Opacity of the Crystalline-Lens yet they were not the first, who made that Observation. For M. Lasnier, an eminent Surgeon of Paris; and who died in 1690, made the same Remarks, forty Years before. And tho' he was countenanced in this Opinion, by Robault, and Gassendus; and that in a little Analysis of Mariotte's, Nouvelles Decouvertes, touchant la Vuë, it was publickly asserted, "That the Oculists had found, that 'there was no other way, of curing that Disorder of the Eye, called a Cataract, but by depressing the Crystalline,' &c. Yet it was not sufficient, to gain it any Esteem, in the World."

The several observations made toward the end of the seventeenth century and in the beginning of the eighteenth, by different men who sought to learn what the substance was which they had couched, are clear evidence of the new spirit of scientific inquiry which had finally taken hold of the clinical ophthalmologist and the physician. There is knowledge of no such attempts in the millenium that preceded these investigations.

Morgagni (1682-1771), professor at Padua (1715-1771), in his seventy-ninth year published his "immortal work ["De sedibus et causis morborum per anatomen indagatis" [19]] constituting the true foundation of modern pathological anatomy in that, for the first time, the records of post mortem findings are brought into correlation with clinical records on a general scale." (Hirschberg,[4] volume 14, part 1, page 480.) He dealt with a great variety of ocular diseases and their pathologic appearances. He collected rare observations that had been published in the sixteenth and seventeenth centuries and added his own on the lens and the vitreous, on the optic nerve, etc. Morgagni reported Valsalva's observation that the cataract depressed by couching is always the lens.

The first work dealing specially with the eye, however, is that of Wardrop,[20] first published in Edinburgh in 1808 and republished, together with a second volume, in 1819. No better introduction to this admirable work can be given than that furnished by the author himself: "No attempt has yet been made in this country to treat of the pathology of the human eye." He cited the works of Richter, Beer, Scarpa and others but declared:

> None of these authors have delineated the morbid changes of structure which they have described: A few drawings only are to be found in the works of Beer and Scarpa. . . . The opportunities which the eye affords to the pathologist, from the variety in its structure and situation, of discriminating all its morbid changes, and of observing their progress, renders it peculiarly interesting. . . . Its diseases claim the most patient investigation, and deserve the minute attention of medical men. It is only by continued attention, and patient investigation of the changes produced by disease in all the organs, which compose the human body, that we can expect to enlarge the knowledge of the morbid anatomy of the eye . . . that we can arrive at any general conclusions.

Wardrop's distinguished contemporary Vetch [21] (page 10) wrote: "The honour is justly due to Mr. Wardrop for having first applied the doctrine of modern pathology to diseases of the eye."

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19. Morgagni, J. B.: De sedibus et causis morborum per anatomen indagatis, Venice, ex. typog. Remondiniana, 1761.

20. Wardrop, J.: Essays on the Morbid Anatomy of the Human Eye, Edinburgh, G. Ramsay & Co., 1808; ed. 2, London, A. Constable & Co., 1819, vol. 1; 1820, vol. 2.

21. Vetch, J.: A Practical Treatise on the Diseases of the Eye, London, G. & W. B. Whittaker, 1820.

The illustrations of the work are worthy of the highest praise given to the artist: "He has combined the art of the painter with the skill of the anatomist; and as he has taken the trouble to retouch all the impressions of the plates there is a truth and accuracy preserved in the colouring, which is seldom met with in works of this kind."

Wardrop's work was followed through the nineteenth and into the twentieth century by a long line of studies and comprehensive works marking the growing knowledge of this third fundamental branch of ophthalmology.

I need but mention Schoen [22] ("Handbuch der pathologischen Anatomie des menschlichen Auges," 1828); Dalrymple [23] (Pathology of the Human Eye," 1849-1852); Sichel [24] ("Iconographie ophthalmologique," 1852-1859); Ruete [25] ("Bildliche Darstellungen der Krankheiten des menschlichen Auges," 1854-1860); Heinrich Mueller [26] (1820-1864), whose collected works were published after his death by Becker, in 1872; Pagenstecher and Genth [27] ("Atlas der pathologischen Anatomie des Augapfels," 1875, translated into English by Gowers); Wedl and Bock [28] ("Pathologische Anatomie des Auges," 1886), and Parsons [29] ("Pathology of the Eye," 1904-1908). Many other workers might be added to the list.

I have hurriedly passed over the paths which have revealed the course of discovery of the anatomy of the eye, of the physiology of vision and of the pathology of the eye. They were opened up in this order because it was essential that the first path be cleared so that the second could be found and the first two so that the third could be reached. In this review one is struck by the steady progress, and one sees the earnest effort to study and to understand the structure and the functions of the organ of vision—one finds it inspired by the spirit that manifested itself in the other sciences, in astronomy, in physics, in chemistry, in the exploration of unknown continents.

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22. Schoen, M. J. A.: Handbuch der pathologischen Anatomie, des menschlichen Auges, Hamburg, Hoffmann u. Campe, 1828.

23. Dalrymple, J.: Pathology of the Human Eye, London, J. Churchill, 1852.

24. Sichel, J.: Iconographie ophthalmologique, Paris, J. B. Baillière & fils, 1852-1859, vols. 1-2.

25. Ruete, C. G. T.: Bildliche Darstellungen der Krankheiten des menschlichen Auges, Leipzig, B. G. Teubner, 1854-1860, vols. 1-6.

26. Mueller, H.: Gesammelte und hinterlassene Schriften zur Anatomie und Physiologie des Auges, Leipzig, Wilhelm Engelmann, 1872.

27. Pagenstecher, H., and Genth, C. P.: Atlas der pathologischen Anatomie des Augapfels, Wiesbaden, C. W. Kreidel, 1875.

28. Wedl, C., and Bock, E.: Pathologische Anatomie des Auges, Vienna, C. Gerold's Sohn, 1886.

29. Parsons, J. H.: Pathology of the Eye, London, Hodder & Stoughton, 1904-1908, vols. 1-4.

The practice of ophthalmology is an ancient one but was long in the hands of ignorant laymen equipped with a minimum of traditional training. Kepler found an excuse for Plater's ignorance of optics *because he was a physician.* (Hirschberg,[4] volume 13, page 425.)

Franco the surgeon, whom I shall mention later, complained that "some physicians have contempt for the couchers; it would be well if physicians had some real knowledge of these matters." (Hirschberg,[4] volume 13, page 325.) It is not surprising that many years passed before surgeons and physicians took notice of the great discoveries in anatomy and in physiology.

CLINICAL OPHTHALMOLOGY

The first university clinician to teach Kepler's doctrine of refraction was the famous Boerhaave; the year was as early as 1708, but this was a century after Kepler's work was published!

About the same time Maître-Jan said that the surgeon was so ignorant about optics that he did not even know the terms used.

As late as 1640 Lazare Rivière, a learned professor of Montpellier, repeated the ancient notion that the crystalline lens is the seat of the image of external objects. Hirschberg stated (volume 17, page 308):

> The physicians and surgeons of scholarship in the sixteenth and seventeenth centuries had no experience in treating the eye, and those who had experience were quacks and barber-surgeons without learning. The former treated eye disease but rarely, or refused entirely to do so, and especially did they refuse to perform the operation for cataract.

Let me quote Castiglioni (page 550)[30]:

> The progress of surgery during the 17th century was neither so marked nor so important as might be supposed from the advances made in anatomy and pathology. . . . Also the surgeons of the period lacked the scientific preparation that was even then available. Although the situation was improving daily, the abyss that separated them from the physicians was still considerable.

The best surgeon-oculist of the period was Pierre Franco (1500-1561), a true barber-surgeon, who was equally famous for his hernia operations, his operations for stone in the bladder and his cataract couchings. His works appeared in twelve volumes, of which the fourth deals with the eye. He was a great operator for cataract and wrote that he had operated on 200 patients and that 9 out of 10 had been cured—figures which Hirschberg called the first statistics on cataract operations! Still more interesting is his statement that had he to choose between abandoning operations for cataract and abandoning the whole of surgery he would choose the latter!

30. Castiglioni, A.: A History of Medicine, translated from the Italian and edited by E. B. Krumbhaar, New York, Alfred A. Knopf, Inc., 1941.

There is reason for giving attention to the works of this period, for I have to cite them in order to show the progress made in clinical ophthalmology in the seventeenth and eighteenth centuries. It is significant that the first treatises on diseases of the eye in German, in French and in English appeared near the end of the sixteenth and early in the seventeenth century, for this fact indicates the contemporary awakening of interest in the subject.

Bartisch's [31] (1535-1606) large volume was published in Dresden in 1583. It has the earmarks of the clever barber-surgeon without medical training but not without ingenuity. The latter is best seen in the numerous illustrations, which form the most interesting feature. The descriptions of disease conditions are meager. Bartisch found that poor vision results from old age, poor food, glare, reading fine print, drinking and excessive venesection. With regard to disease he showed little advance except in the description of the operative treatment of the eye. He inveighed against the use of spectacles as injurious, "for one sees better without placing anything before the eyes." He offered advice on how to avoid using them and how to discard them. He gave abundant evidence of the influence of witchcraft and magic. Hirschberg was willing to disregard his limitations because of his period and considered him able, earnest and ambitious, a good observer, a clever and courageous surgeon and an inventor of instruments.

Jacques Guillemeau (1550-1613), his contemporary, a man of education, was a pupil of Ambroise Paré and one of the most celebrated surgeons of his time. He wrote works on anatomic tables (1585), French surgery (1594) and obstetrics (1609) and, what interests ophthalmologists especially, "Traité des maladies de l'oeil, qui sont en nombre de cent treize ausquelles il est suject," [32] which appeared in 1585 and was dedicated to Paré.

Guillemeau's small book follows the work of the older surgeons. His descriptions of diseases are clearer and fuller and include causation, signs and treatment; they are well arranged. A contemporary surgeon described it as "a treatise of the diseases of the eye in which you have included not only what the ancients have written but also those rare cases which you have observed." (Hirschberg,[4] volume 13, page 330.) Bannister's [33] treatise (1622) is but an English translation of Guillemeau's.

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31. Bartisch, G.: Augendienst, Dresden, M. Stöckel, 1583.

32. Guillemeau, J.: Traité des maladies de l'oeil, qui sont en nombre de cent treize ausquelles il est suject, Paris, C. Massé, 1585.

33. Guillemeau, J.: A Treatise of One Hundred and Thirteen Diseases of the Eye, the Second Time Published, with Some Profitable Additions of Certaine Principles and Experiments by Richard Banister, London, T. Man, 1622.

The real advance was not in new contributions to knowledge but in the fact that able and clever men interested themselves in diseases of the eye and devoted themselves to this branch of medical science.

In 1620 Fabricius ab Aquapendente published his "Opera chirurgica" [34] and in 1640 Rivière, of Montpellier, his "Praxis medica." [35] Both men expressed themselves as opposed to couching. The latter urged surgeons not to perform the operation because "it is rarely successful and should be left to the wandering oculist." (Hirschberg,[4] volume 13, page 287.)

The medical science of this period, it must be remembered, was completely under the aegis of humoral pathology, and the few works dealing with diseases of the eyes accord with this conception.

It is with amazement that one observes the sterility of the seventeenth century in clinical ophthalmology. The works on surgery contain a poor rehash of the past. The sterility is even more striking when one remembers that this was the century of Galileo, Newton and Bacon, Descartes and Leeuwenhoek in the other sciences and of Harvey and Sydenham in medicine. The surgeons were generally not interested, and the oculists were ignorant laymen. But there was too intense a scientific ferment to leave the field unaffected.

The eighteenth century introduced the new spirit of enlightenment into clinical ophthalmology. More men of education devoted themselves to its study, with resulting great progress in the science and the art. No phase illustrates this better than does cataract. This disease was regarded in the ancient Greek period and during the Arabian as due to the effusion from the brain into the eye of a humor which formed an opaque coagulum, "a film of membranous substance," between the iris and the lens. Together with this pathologic conception, the method of couching the cataract was handed down through the ages for the relief it gave. The operation was done largely by quacks, as has been mentioned. Not until the beginning of the eighteenth century was the truth discovered. The account as related by O'Halloran in 1750 has been quoted. It gives clear evidence of an entire change of method in clinical observation and study.

It is interesting to read the criticism of so wise a contemporary as Boerhaave [36] concerning the controversy about cataract: "The ancients proved their statements with simple logic but without dissection of eyes, diseased or operated upon, but on the contrary were satisfied with external signs only. By such means our daily experience proves to be deceptive!"

34. Fabricius ab Aquapendente, H.: Opera chirurgica, Frankfurt, excud. N. Hoffmannus, imp. I. Rosae, 1620.

35. Riverius [Rivière], L.: Praxis medica, Paris, 1640.

36. Boerhaave, H.: Praelectiones publicae de morbis oculorum, Göttingen, A. vanden Hoeck, 1746.

It was in France that the progress was most evident. Tenon said that "surgery had made greater progress there in a half century than in all the centuries since Hippocrates." (Hirschberg,[4] volume 14, part 1, page 2.)

Brisseau [17] was a physician, not an oculist. His work is the first clinical study which brought advancement to one of the three underlying scientific branches of ophthalmology, the pathology of the eye.

Maître-Jan published his "Traité des maladies de l'oeil" [37] in 1707. He gave as a reason for his undertaking to write the treatise "because very few practitioners have written on the diseases of the eye and among the later authors most have done nothing but to collect what they have found among the ancients, without contributing anything of their own except perhaps some Greek names of diseases which confuse and hinder rather than instruct."

The work of Maître-Jan is a revelation of a new spirit; it is the spirit of Vesalius and Kepler entering into the field of clinical ophthalmology. Maître-Jan was a surgeon and a scientist, but his chief interest was the diseases of the eye. His large work of 576 pages not only takes up the entire subject of the ophthalmology of the period in great detail but gives a large number of case reports. It is complete and systematic and in a large measure based on his own experience. He made careful anatomic studies of the eye and numerous experiments in the problems of vision. Because of his independent spirit in the observation and study of diseases, his work deserves special attention.

Throughout he shows that:

> He was guided in his work by the principle that an anatomist should not write anything but what he himself sees, or at least considers so probable that it cannot be denied. Thus [he] has studied all parts of the human eye and also the same found in the eyes of animals. . . . When because of their subtility [in the human eye] their structure cannot be disclosed, [he] found recourse to those of animals to serve [his] purpose.
>
> When [his] views are not in accord with the anatomists [he] hopes for fair judgment!
>
> [He] was more concerned to prove his own views than to contradict those of others.

There are interesting discussions of problems such as the nutrition of the transparent media without their discoloration by the blood. This is brought about by the ciliary body's acting as a filter!

He wrote apologetically of his long chapters on the refraction of the eye:

> I may perhaps be blamed for having inserted too many optical experiments. However, when one considers how little surgeons in general understand about optics, that they scarcely know the terms, there is reason to believe that I have

37. Maître-Jan, A.: Traité des maladies de l'oeil, Troyes, J. le Febure, 1707.

not told them too much for an understanding of the function of the parts of the eye and the incidents that arise in the treatment of diseases of the eye.

A single example of Maître-Jan's spirit of scientific investigation may be given. In the chapter on tremulous cataracts he wrote that he had long been unable to understand the underlying condition. Finally, in 1691, he saw a tremulous cataract in the eye of a cow. He obtained the eye, and he gave the following description:

When he held it in his hand, the slightest movement caused the lens to tremble. He opened it by separating the cornea at the margin, holding it with this part above so that the contents of the eyeball would not escape; on removing the iris he was able to see the lens floating in the fluid with a fine membrane and fibres at its margin round about.

[He] then incised the sclera back to the entrance of the optic nerve and discovered that the retina was entirely separated from the choroid, attached only at the optic nerve and in front of the ciliary body, thus representing a cone with its apex at the optic nerve.

Within this cone he found fine membranous fibres which appeared to be remains of the vitreous which had otherwise disappeared entirely.

This is the first mention of detachment of the retina. One must not fail to note the frequency of Maître-Jan's studies of the comparative anatomy of the eye. "I have mentioned descriptions of the eyes of animals, which are not to be despised, since they are also affected with such diseases."

Maître-Jan in a respectful criticism of the ancients and of those who preceded him referred to matters in which they were in error:

For example their view of the function of the lens and the manner in which the sight is brought about led them to a false conception of cataract and other diseases of the eye. I may state that I myself should entertain the same view that the lens was the chief organ of sight. But though they were ignorant of the true nature of cataract, they invented such a clever operation that its purpose was satisfactory, which is still practiced by oculists today with happy results and which will continue to be practiced in the future as long as surgery lasts in the world.

He did not flatter himself that his work was perfect and that it exhausted the subject but rather believed that other matters would be discovered, and he called on eager surgeons "not to neglect to make known what they discover as I too shall do in whatever noteworthy I meet with."

He considered the discussion bearing on the seat of cataracts so important that his book contains copies of the treatises published in the Academie Royale on the subject. Antoine Maître-Jan may well be regarded as the pioneer in modern clinical ophthalmology. He opened up a path in which numerous earnest and talented students followed throughout the eighteenth century. Of these, one must not fail to mention St. Ives.

It is interesting that de St. Ives, of Paris (1667-1726), whose "New Treatise of the Diseases of the Eyes" [38] first appeared in 1722, wrote that authors did not agree about the nature of cataracts: "This diversity of opinion must not be imputed to the obstinacy of these authors. It may . . . be ascribed to the few occasions they have had of undeceiving themselves, for . . . we shall find both Crystalline and Membranous Cataracts . . ."

But under the head of "true Cataracts" he stated: "Most moderns define true Cataract to be the Crystalline Humours affected and not a Membrane formed in the Aqueous Humour; as the Ancients described it. I adhere to the modern . . ."

It must be borne in mind, however, that de St. Ives held many traditional views. He found explanation of certain visual disturbances in "an unequal Influx of the Animal Spirits," and in his chapter "How to Be Exempted from the Use of Spectacles" one reads: "The good [i. e. not near sighted or far sighted] sight is often weakened by a redundant serosity which perpetually fills some Peoples Eyes" and that "Remedies which evacuate the Pituita from the brain, such as purges and smoaking tobacco, are serviceable in this Disorder of the Sight."

De St. Ives couched cataracts, but he removed one dislocated into the anterior chamber through an incision in the cornea.

His efforts to classify ophthalmia resulted in the following division: the dry, the moist, that following a "defluxion," the "ophthalmia with dry film," that "which seizeth the globe toward the temples," that which is "attended by pimples," etc. There are two which are of special interest. "Erysipelatous ophthalmy" is clearly the earliest recognition of ophthalmic herpes zoster: It "causes violent pains and heat both in the eyes and in the head. The neighboring parts of the eyes, as the temples, the forehead and the nose, are covered with scales and scabs that leave, when they fall off, marks for life, resembling those which come by smallpox." It was more than a century later that Hutchinson recognized the true nature of the condition and likewise noted that it was generally regarded as erysipelatous!

Another, and yet more important, observation of de St. Ives was of "venereal ophthalmy," which he recognized as gonorrheal and of which he had "seen several cases." "In most of them the disease appeared two days after the beginning of a virulent gonorrhea; the matter not running off by its usual passages, was removed to the eye through which there flowed a like matter, which stained the Linnen in the same manner."

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38. de St. Ives, C.: Nouveau traité des maladies des yeux, Paris, P. A. Le Mercier, 1722; A New Treatise of the Diseases of the Eyes, translated by J. Stockton, London, J. Crokatt, 1741.

It will be seen that de St. Ives regarded the ocular inflammation as metastatic.

One other clinical observation of de St. Ives must be pointed out. He described "Ophthalmy of the Choroides . . . in which the inner parts of the eye are inflamed. . . . The conjunctiva is but lightly inflamed; it is attended with a flux of tears. To look at the light is painful to the patient, who feels acute pains toward the top of his head and temples. The pupil is also contracted." This is clearly an early recognition of iritis!

It is interesting to read in de St. Ives's preface:

> I have endeavored to clear some Doubts, which had hitherto prevailed concerning the immediate Organ of Vision, and likewise concerning the various Nature of Cataracts which had not been sufficiently explained by Authors, whose Judgment and Skill were defective from a Want of Experience and due Reflexion; I say farther, this Branch of Surgery has been so much disregarded, that some presumed to treat all those, as Quacks, that made it their chief Employment. Yet this Art has Principles and Rules as certain and as difficult to learn, as any other Branch of Surgery.

In Maître-Jan and de St. Ives one sees the new spirit of inquiry as to differences in appearance and course of diseases. "The ancients, especially the Greeks, did not describe diseases but gave definitions." (Hirschberg,[4] volume 14, part 1, page 379.) This method was now reversed. Maître-Jan and de St. Ives gave clear descriptions of disease.

Maitre-Jan and de St. Ives were keen observers, but it must not be thought that they and their followers broke all the chains of traditional medicine. The theory and the therapy of eighteenth century ophthalmology was still markedly under the influence of the past. De St. Ives wrote:

> The Blood is the Spring of all Ophthalmias proceeding from an inward Cause, Whether the Fault be in the too great Redundancy, or in some acquired bad Quality; such as the Thickness, Viscosity, Acrimony, or too great Rarefaction of the Blood. If the Quality of the Blood be excessive it will be carried in too great Plenty, into the minute Vessels which are spread in the Eye and so produce an Ophthalmy.

Venesection was the panacea. The great change lay in the interest that was awakened in a large number of surgeons in diseases of the eye; some surgeons even limited their activity to ophthalmology. Many were understanding men, such as de St. Ives, the Petits, Daviel, Tenon and Demours, in France; Monro, Pott, Cheselden (who accepted the new doctrine of cataract in 1713 and introduced an operation for artificial pupil in 1729) and Sharp, in England; Heister, in Germany, and particularly Boerhaave, in Holland, who gave courses of lectures and whose pupils spread the new doctrines throughout Europe.

Gataker,[39] an English surgeon, wrote in 1761: "The dispute about the cataract . . . does now no longer prevail. It is the general opinion at present that a cataract is an opacity of the crystalline."

There were still quacks and mountebanks in all lands; in London charlatans swarmed and many wrote books and a new species had developed which have been called the knight errant oculists, such as Chevalier Taylor, Baron von Wenzel and others of that ilk, who flourished in the eighteenth century and left less notorious heirs in the nineteenth.

The discovery of the nature of cataract acted as a great ferment. Its first effect was an intense controversy as to the existence of membranous cataracts; this was due partly to the firm hold of the ancient view and partly to the observation of membranes in the pupillary area resulting from iritis. But the dispute was helpful in directing closer observation of pupillary opacities and in furthering knowledge of the subject of visual impairment. The large number of learned treatises which appeared in the first half of the eighteenth century are evidence of the growing interest. Some works, such as those of Petit presented to l'Academie Royale des Sciences in 1725, 1726 and 1730 on cataract, were of great importance. The greatest effect of this increased interest was the solution of the cataract problem contributed by that great discoverer Jacques Daviel (1693-1726), who introduced the extraction of cataracts in 1752. On the occasion of his third semicentennial anniversary, Dr. A. A. Hubbell, distinguished ophthalmologist of Buffalo, N. Y., gave an excellent commemorative address,[40] from which I have taken a few passages. Daviel was a surgeon and a teacher of anatomy who early in practice showed a predilection for the eye and operated for cataracts by couching.

> He energetically availed himself of the anatomic material which was at his disposal, supplementing his work on the eyes of the living with experiments and operations on those of the dead. He acquired much skill as a surgeon-oculist, and soon gave himself up exclusively to ophthalmic practice.

But he later wrote that this operation

> has always seemed to me to be very doubtful. . . . It is only after many experiments performed on the eyes of cadavers and a large number of operations on those of the living, with the view of perfecting the method of depressing cataract, that I have learned all the dangers and all the points of doubt which one can have in this matter. In multiplying my experiences and observations I have been forced to recognize, at last, that it is far from being a fact that this operation is as certain and as easy as many people have believed, and as I believed, myself, when I began to practice it. I owe this confession to the truth, although

39. Gataker, T.: An Account of the Structure of the Eye, London, R. & J. Dodsley, 1761.

40. Hubbell, A. A.: Jacques Daviel and the Beginnings of the Modern Operation of Extraction of Cataract, J. A. M. A. **39**:177 (July 26) 1902.

it seems, at first, to do some wrong to the art to which I have been entirely devoted for about eighteen years, and which I have resolved to practice exclusively the rest of my life.

Daviel knew that both de St. Ives and Petit "had, in 1707 and 1708, each extracted a lens through an incision in the cornea which had become dislocated accidentally, into the anterior chamber. . . . Soon . . . an opportunity was afforded him to put to the test . . . his first predetermined and prearranged extraction." The result was successful.

Further trials gave him more and more assurance of its superiority over the old operation of depression, and finally, in 1750, he had sufficient experience to cause him to resolve, thereafter, not to operate except by extraction. His cases grew more and more numerous. . . . At Rheims, in September and October, 1751, he performed forty-three operations. These operations were reported to the Royal Academy of Surgery of Paris soon afterward and created great excitement. A few indorsed the new method and many opposed it. But Daviel held firmly to it, and in 1752 . . . he considered it sufficiently perfected and sufficiently fortified by good results to submit it to the world. This he did through the learned and discriminating body, the Royal Academy of Surgery of Paris. . . ."[41]

In 1756 he was able to report on 434 operations with 50 failures, or 11.3 per cent. His studies were an example of careful experiment to choose the most satisfactory method. Daviel's contribution is one of the great ones which medical science and art have bestowed on humanity. In the almost two centuries that have elapsed ophthalmologists have followed his course in the endeavor to improve and make safer this cure of blindness.

Daviel too had his opponents, and even after his death a surgeon as distinguished as Percival Pott wrote disparagingly of the "operation of fashion." Bell was unfavorable to it, and, even in the early nineteenth century, Scarpa[42] maintained that

observation and experience, the great teachers in all things, seem to have pronounced in favor of the ancient method of treating the cataract, that of depression. . . . I have for a considerable time laid aside the method of treating the cataract by extraction and have applied myself entirely to the practice of depression and I see continually great reason to be satisfied with the choice which I have made.

I have indicated that the active scientific spirit of the times in great measure accounts for the outburst of scientific productivity in ophthalmology in the eighteenth century. But in retrospect one must recognize that the very activity of the interest awakened by the discovery of the

41. Daviel, J.: Sur une nouvelle méthode de guérir la cataracte par l'extraction du crystalin, Mém. Acad. roy. de chir. **2**:337, 1753.

42. Scarpa, A.: Practical Observations on the Principal Diseases of the Eyes, translated from the Italian with notes by James Briggs, London, T. Cadell & W. Davies, 1806, pp. 352-353.

seat of cataract in the lens and the violence and the duration of the controversy were likewise important factors.

The notable advances of ophthalmology in the eighteenth century were the discovery of the seat of cataract in the first half and of extraction in the second and the advance of clinical ophthalmology by Brisseau, Maitre-Jan, de St. Ives, Daviel and others. It will be seen that the path of clinical ophthalmology had been greatly widened and extended. But it may also be observed that the widening was brought about through the close approach of the path of clinical ophthalmology to the paths of anatomy, of physiology and of patholgy.

One is thus prepared for their union in a wide road—where the way is common to all though the special interests are individual. The nineteenth century now opens with Beer and with the creation of the first chair of ophthalmology, at the University of Vienna.

The works of Beer are a landmark indicating the progress. In his voluminous "Lehre von den Augenkrankheiten," [43] covering over 1,300 pages, he produced a systematic and valued work. This appeared in English in 1821 in abbreviated form, covering only 600 pages.[44]

It is not free from the "metaphysical confusion" which Osler pictured as a quality of eighteenth century medicine. But while this underlies the classification, which makes its reading heavy, his description of diseased conditions is clear and vivid and his observations correct, as are his drawings. There is no better gage of clinical ophthalmology of this period, for his popularity is known. His lectures and his work exercised a profound influence on the growing numbers of students who flocked to Vienna, and they spread his teachings throughout Europe. It was Beer who gave the first satisfactory description of syphilitic iritis and advised mercurial treatment.

It is interesting to note Beer's changes in the assumed causation of ophthalmias. He divided ophthalmias into two classes, the idiopathic, i. e. those in otherwise healthy persons, and the sympathetic, among which he placed the variolous, venereal, cachectic, gouty and scrofulous forms and those accompanying measles, scarlatina, scurvy, etc.

Beer described arthritic iritis with intense pain, contracted pupil and inflammatory exudate on the iris and a condition in which the pupil becomes dilated and oval and the iris pushed up to the cornea, clearly acute glaucoma. In another place he spoke of an eyeball as hard as flint. He treated glaucoma, under the heading "Opacity of the Vitreous and Green Cataract," as belonging to the class of arthritic ophthalmias and described the oval and dilated pupil, the venous congestion and the secondary cataract, but here he did not mention increased tension.

43. Beer, G. J.: Lehre von den Augenkrankheiten, als Leitfaden zu seinen öffentlichen Vorlesungen entworfen, Vienna, Camesina, Huebner u. Volke, 1817.

44. Beer, G. J.: A Manual of the Diseases of the Human Eye, Glasgow, 1821.

Beer's method of intracapsular extraction of cataracts with the special Beer knife, which he introduced, was most popular for half a century, until superseded by von Graefe's method.

With Beer, clinical ophthalmology attained its modern dignity.

Beer's influence is seen best in the splendid work of Mackenzie, who followed him in accurately describing diseases of the eye and made notable advances. In this country George Frick [45] spread Beer's gospel in concise and clear form and without the encumbrance of his philosophic disquisitions.

During the latter half of the eighteenth and far into the nineteenth century the subject of purulent ophthalmia, and especially the problem of contagion, aroused intense interest. Wide differences of view found expression. A brief review will afford evidence of the slow progress in the discovery of the truth. The difficulty was not lack of serious students or their failure to gather observations. It was chiefly the false philosophy of disease, which hindered the proper interpretation of the observations made.

It is interesting to look back through the centuries to find the early explanation of the transmission of ophthalmia from one sufferer to another. It was solved to the satisfaction of Maimonides [46] in this manner: "A person who has never seen ophthalmia, when he sees a case will have his eyes become filled with tears. If he continues to gaze upon it he, himself, will be affected with ophthalmia."

Fracastorius in 1546 in his great work on contagion [47] said, "There is a kind of ophthalmia with which the sufferer infects every one who looks at him."

The reluctance to accept the theory of contagion was expressed more definitely almost two hundred years later, for the Louvain professor Plempius [15] (1632) stated, in a chapter on diseases of the conjunctiva:

> Ophthalmia is contagious according to the consensus of all writers. Why then do not the oculists and quacks suffer constantly, who day by day take care of and treat and examine those [suffering] with eye diseases? I am very strongly of the opinion that the imagination accounts for the contagion of the diseases. Therefore vision is most damaged in this manner if he who inspects diseased eyes is apprehensive of infecting himself; while oculists who are not in fear . . . are not infected.

With regard to venereal ophthalmia and the question of contagion opened up by de St. Ives in 1722, this writer, as has been noted, attributed ophthalmia to metastasis, and his view long held sway. In

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45. Frick, G.: A Treatise on the Diseases of the Eye, Baltimore, F. Lucas Jr., 1823.

46. Maimonides: Aphorisms, Bologna, 1489, chap. 24, sect. 19.

47. Fracastorius, H.: De contagione et contagiosis morbis et eorum curatione, libri III, Venice, 1546; Translation and notes by W. C. Wright, New York, G. P. Putnam's Sons, 1930.

a little less than twenty years Astruc [48] furnished definite evidence of the direct autoinfection of the eyes with gonorrheal pus. The case is famous:

> . . . With the gonorrheal ophthalmia ought properly to be classed that virulent one, propagated as it were by inoculation, a rare but evident instance . . . for nothing in the world can be clearer than this case. A young man had accustomed himself for a long time to wash his eyes in his own urine warm, every morning to strengthen his sight. Unluckily he was infected with a violent gonorrhea, and . . . continued his former practice. However the urine impregnated with the venereal poison, communicated the contagion to the conjunctiva and eyelids; whereby a violent venereal ophthalmia was brought on, with a sharp involuntary discharge of tears and purulent matter, both which were at last perfectly cured by the same remedies, which were used in curing the gonorrhea.

It is hard to explain the general reluctance to accept Astruc's evidence.

As early as 1750 Quelmalz (1696-1758), who was professor of surgery, anatomy and other branches at Leipzig, gave an address in which he proclaimed for the first time in medical history that the ophthalmia of the newborn is due to gonorrheal infection of the mother. Like de St. Ives and all his contemporaries he regarded the disease as metastatic, a view that endured far into the next century. Hirschberg pointed out with great emphasis how far ahead of his period Quelmalz was, for Beer of Vienna, half a century later, still assigned as the cause of the ophthalmia of the newborn polluted atmosphere, exposure to light, washing the eyes with rough sponges and pouring cold water over the infant's head in baptism, views still later repeated in well known textbooks.

I have mentioned these few references to a long discussion. The confusion resulted from various factors. Foremost was the assumption that syphilis and gonorrhea were different manifestations of the same venereal disease.

It must be borne in mind that Benjamin Bell [49] in 1792 first "pointed out the causation and clinical differentiation between gonorrhea and syphilis."

The view of de St. Ives led to the belief that suppression of gonorrhea would result in the metastatic inflammation of the eye, and one may read in Beer [43] (page 547):

> From the first moment the physician must give his attention to reestablishing the urethral gonorrhea . . . the most successful and surest way is infection with a bougie smeared with gonorrheal pus from another individual.

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48. Astruc, J.: De morbis venereis libri novem, Paris, G. Cavelier, 1740, book 3, chap. 3; A Treatise of Venereal Diseases, in nine books, translated by W. Barrowby, London, printed for W. Innys and others, 1754, vol. 1, p. 306.

49. Bell, B., cited by Holcomb, R. C.: The Antiquity of Congenital Syphilis, Bull. Hist. Med. **10**:155, 1941.

We hear now and then of an ophthalmia produced by gonorrheal pus reaching the conjunctiva. I have often had the opportunity to observe such but in all it was only a simple inflammation that resulted, which disappeared under ordinary treatment.

But he conceived it possible that if the patient was a weak person with pituitary cachexia gonorrheal ophthalmia might develop!

Beer's renowned contemporary Scarpa (1752-1832) wrote:

This disease, as it is almost commonly met with in infants, a little after their birth, or attacks adults in consequence of a sudden suppression of the violent gonorrhea, or of a translation of the venereal poison in some other manner to the eyes, is called in the first case the puriform ophthalmia of infants, in the second the acute gonorrheal ophthalmia.

Like Beer, Scarpa taught that if gonorrheal matter was applied to the eye it excited only a slight degree of inflammation.

The controversy continued vehemently throughout the first quarter of the nineteenth century. Some writers found it necessary to change their point of view, for example Ware.[50] In 1780 he recognized only a venereal (syphilitic) ophthalmia "produced by so active a poison, that when it has once entered the habit, no part can be said to be exempt from its malignant influence." He found no reason for regarding purulent ophthalmia as metastatic gonorrhea. "Such a complaint as St. Ives describes may happen as well during the time that a person has a gonorrhea as at any other."

Twenty-four years later he wrote:

It has been said, that if any of the matter which passes from the urethra, in a gonorrhea, be applied to the eye it will bring on an ophthalmy, accompanied with a discharge similar to that which previously took place from the urethra. Probable as this may appear in speculation, I have found it very difficult to ascertain the fact.

But he added as a footnote:

At the same time that I am correcting for the press [1805] the fourth edition of this tract on the ophthalmias, I am consulted in a case which strengthens the opinion of those who think the purulent ophthalmia is occasioned by the application of diseased matter to the eye itself. Two female children, the eldest only five years of age, were attacked with a purulent coloured discharge from the vagina, without any previous indisposition, or any probable cause that could be assigned for it. The surgeons recommended a vitriolic lotion to be injected, which in a short time removed the disorder. The operation of injecting the lotion was performed by the mother of the children; and, about a week after it had been used, the mother, who as well as the father was perfectly free from any complaint, was attacked with an inflammation of the right eye, the conjunctiva of which swelled very rapidly; and it was soon accompanied with a profuse discharge. . . . At the time I saw her the cornea was on the point of bursting, which happened that very day, totally destroying the eye as an organ of vision. . . .

50. Ware, J.: Remarks on the Ophthalmy, Psorophthalmy and Purulent Eye, London, C. Dilly, 1780, p. 20; Chirurgical Observations Relative to the Eye, London, J. Mawman, 1805, vol. 1, pp. 32-33.

He wisely added:

It therefore becomes necessary, in all such cases, in order to prevent the possibility of communicating infection, that the handkerchief or cloth, applied to the patient's eyes should be confined to his use alone; and such caution should be especially observed in families where there are children; as they are more likely to receive injury in this way than grown persons.

Noble [51] wrote in 1800:

I trust we shall not be going too far in declaring that those cases which have been said to be owing to a suppressed gonorrhea have been caused by cold. It only happens in those persons who have naturally weak eyes (or suffer from blows, foreign bodies, etc.)

There is another method by which it is said the eye may be affected with gonorrhea and that it is from the patient conveying, by his fingers, or any other means, the matter . . . to the eye. . . .Were it possible for the eye to be affected in that manner, other parts would alike be exposed to its baneful action, and what a fruitful source of misery would be let in upon mankind.

In Briggs's English translation of Scarpa (1806) there is a letter from Pearson, an authority in the treatment of venereal syphilis, in which he said:

Although I am fully disposed to treat the talents and accuracy of Professor Scarpa with the utmost deference, yet I cannot help entertaining some doubts of the propriety of assigning the gonorrhea as a cause of ophthalmia since during a pretty extensive experience of twenty-five years I have never seen a single instance of an inflammation of the eyes which was evidently derived from a gonorrhea.[52] The puriform ophthalmia of infants was within my recollection generally regarded as an indication of a venereal taint; and much unnecessary distress was often excited in families, and very improper treatment was frequently pursued, in consequence of this erroneous opinion. I conceive that mistakes in these cases are not very common at this time.

The outbreak of a severe epidemic of purulent ophthalmia in England in the early years of the nineteenth century greatly intensified the interest in this subject, not of ophthalmologists alone but of army surgeons, of Parliament and of the public.

Edmondston [53] published in 1802 "An Account of an Ophthalmia Which Appeared . . . in 1802; with Some Observations of the Egyptian Ophthalmia" and in 1806 "A Treatise on the Varieties and Consequences of Ophthalmias, with a Preliminary Inquiry into Its Contagious Nature," which he supported with convincing proof. But

51. Noble E. M.: A Treatise on Ophthalmy, and Those Diseases Which Are Induced by Inflammations of the Eyes, Birmingham, Swinney & Hawkins, 1800.

52. John Hunter, as cited by Hirschberg [4] (volume 14, part 4, page 140), expressed himself in a similar manner.

53. Edmondston, A.: A Treatise on the Varieties and Consequences of Ophthalmias, with a Preliminary Inquiry into Its Contagious Nature, Edinburgh, W. Blackwood, 1806; An Account of an Ophthalmia, Which Appeared in . . . 1802, London, J. Callow, 1802.

he also contended that the disease was "capable of being communicated by looking at eyes already affected with it, and gives some cases where the patients ascribed the origin of the disease to that source." (Vetch,[54] page 3.)

"An Account of the Ophthalmia Which Has Appeared in England Since the Return of the British Army from Egypt" was published in 1807 by Vetch,[54] an army surgeon. His observations convinced him that it was

> communicated by the local application of the infectious matter. . . . The concurrence of the presumptive proofs of the infectious nature, of the discharge from the eyes, is so complete, as in a great measure to supply the want of the positive experiment, which I believe no person will have the rashness to make upon himself or the cruelty to inflict upon others.

Years later he wrote an account of Egyptian ophthalmia (Vetch,[21] volume 2, page 179): "I first established that the communication of the disease was exclusively produced by the application of the discharge from the eyes of the diseased to those of the healthy."

Vetch's experiments and experiences in dealing with this disease by sanitary measures and isolation gave brilliant results.

The following dictum is impressive: "The supposition of actual metastasis of the inflammation . . . I believe is seldom met with but in books."

The following account is interesting:

> In the case of a soldier received in a very advanced state of Egyptian Ophthalmia, in whom destruction of the cornea had to a certain extent taken place, I took occasion to represent the possibility of diverting the disease from the eyes to the urethra by applying the discharge to the latter surface, and he requested that this experiment, or any other, might be tried . . . and accordingly some of the matter taken from the eyes was freely applied to the orifice of the urethra. . . . No effect following this trial . . . it was repeated in some others, all labouring under the most virulent state of the Egyptian disease; and in all the application was perfectly innocuous. . . . But in another case, where the matter was taken from the eye of one man labouring under purulent ophthalmia and applied to the urethra of another, the purulent inflammation commenced in thirty-six hours afterward and became . . . a very severe attack of that disease.
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> From the result of these cases I could no longer admit the possibility of infection being conveyed to the eyes from the gonorrheal disease of the same person. Some time after this the improbability, or rather impossibility, of this effect was rendered decisive by a hospital assistant who, with more faith than prudence, conveyed the matter of a gonorrhea to his eyes without any affection of the conjunctiva being a consequence. From this time I was led to look for an explanation of the connexion subsisting between gonorrhea and ophthalmia arising in the same person in some peculiarity of the constitution and to conclude that the disease is an extension of an inflammation which first shewed itself in the urethra

54. Vetch, J.: An Account of the Ophthalmia Which Has Appeared in England Since the Return of the British Army from Egypt, London, Longman [and others], 1807.

and of which the different structures of the eye are liable to participate in common with many other parts.

I have cited this long passage to show how false conclusions are formed from well intentioned experiments.

Vetch reported that two surgeons had the matter conveyed by accident to their eyes but by careful washing it was prevented from producing the disease (Vetch,[21] volume 2, page 74). He reported figures, which best show the dreadful character of the epidemic. In a battalion of a little more than 700 men, 636 men had ophthalmia in the course of one year (1805-1806); of these, 50 lost the sight of both eyes and 40 that of one eye (Hirschberg,[4] volume 14, part 4, page 69). While in a hospital for the children of soldiers, McGregor, in 1804, had 629 cases in a population of 1,200; 6 patients lost the sight of both eyes and 12 that of one eye (Hirschberg,[4] volume 14, part 4, page 76). It appears that there was universal agreement concerning one matter—acceptance of treatment by venesection.

Other interesting and dangerous experimental investigation was not overlooked. Cases of accidental transference of gonorrheal matter to the eyes were reported by others beside Astruc (Hirschberg,[4] volume 14, part 1, page 356).

Mackesy (Hirschberg,[4] volume 14, part 4, page 76) published "An Experiment to Ascertain the Effects Produced in Sound Eyes by Application of the Discharge of Ophthalmia in Its Different Stages" (1816). He applied secretion taken from the inflamed eyes of 4 soldiers to his own by moistening a piece of linen with it; no inflammation resulted. He therefore opposed the theory of contagion.

Guillie (1780-1865) in 1819 took pus from the eyes of children "in the second stage of contagious ophthalmia" and placed it in the eyes of 4 blind children. In all, ophthalmia developed between the second and the fourth day, and all were cured. But Guillie's experiments do not arouse great confidence, because he claimed positive results in a dog, a rabbit and a pig (Hirschberg,[4] volume 14, part 3, page 31). He wrote: "The disease is contagious; most French physicians do not believe this, though the English, German and Italian do." Mackenzie gives a good account of Guillie's work.

Travers [55] in 1820 wrote: "The highly contagious nature of suppurative ophthalmia, whether in the mild or vehement acute form, is sufficiently proved. . . . I have repeatedly seen the most virulent form of the disease produced by accidental translation of the matter of gonorrhea" (pages 97 and 98).

Demours still denied the contagious character of ophthalmia in 1821. "Ophthalmia neonatorum is due to careless treatment of the infant and

55. Travers, B.: A Synopsis of the Diseases of the Eye, London, Longman [and others], 1820.

to exposure to damp and cold air." (Hirschberg,[4] volume 14, part 1, pages 345 to 347.)

Lawrence,[55a] in his work of over 300 pages, advanced markedly beyond Beer. He divided the gonorrheal ophthalmia sharply from the syphilitic. Concerning another matter he was equally definite: "Although these various considerations would lead us to expect that gonorrheal discharge would not affect the eyes of the same individual, we meet in practice with cases from which there is every reason to draw the contrary conclusion." He cited cases of suppression and metastasis: "In none of his cases was there suppression of the urethral discharge. . . . We cannot admit that . . . its origin [is] cessation of discharge."

Mackenzie [56] in 1830 was definite in describing mucopurulent ophthalmia as contagious. He regarded Egyptian ophthalmia as essentially the same disease. He was no less definite in saying: "Vetch regards himself justified in no longer admitting the possibility of infection being conveyed to the eyes from the gonorrheal discharge of the same person. . . . It is remarkable that Dr. Guillie has fallen into the same error."

Middlemore in 1863 still held to the view that gonorrheal ophthalmia cannot be infection from the same person but must come from another. Considerable advances were made, but it was not until 1841 that the final answer was given by an ophthalmologist who was imbued with the clearest scientific attitude and who applied the most careful experimental methods. It is somewhat surprising to find that his name is almost unknown. It is appropriate that this year, which marks the centenary of the appearance of his work, should be noted. The scientist to whom I am referring is Joseph Friedrich Piringer, born in 1800 in upper Austria. He studied in Vienna, was an assistant of Jaeger and later of Rosas and became extraordinary professor of ophthalmology at Graetz, where he founded an ophthalmologic hospital. In 1841 he published "Die Blennorrhoe am Menschenauge." [57] It is a most comprehensive work of 442 pages, dealing with all phases of the subject. It was not to be found in the United States Army medical library until I presented my own copy. Years elapsed before I was able to secure another copy. In 1897 I presented a paper [58] on Piringer, his methods and his investigations, and it is from this that I make the following excerpts:

55a. Lawrence, W.: A Treatise on the Venereal Diseases of the Eye, London, J. Wilson, 1830.

56. Mackenzie, W.: Practical Treatise on the Diseases of the Eye, London, Longman [and others], 1830.

57. Piringer, J. F.: Die Blennorrhoe am Menschenauge, Grätz, F. Ferstl, 1841.

58. Friedenwald, H.: Joseph Friedrich Piringer: His Methods and Investigations, Bull. Johns Hopkins Hosp. **8**:191, 1897.

His experiments on the production of purulent ophthalmia embrace almost one hundred eyes, and this does not include a number of accidental infections which were observed with the same care. The matter with which infection was produced was obtained from eyes affected with different forms of purulent ophthalmia as well as from genital blennorrhoea. All ages and both sexes were found to be equally predisposed.

One of the most interesting chapters is the one on the character of the blennorrhoeic contagion. Though the pus from the conjunctiva causes infection when applied to the eyes of human beings, he was unable to produce any result when he applied it to the eyes of such animals as dogs, cats, hogs, and various birds. Others had claimed that they had produced effects in such cases. Our present knowledge of the immunity of the lower animals to gonorrhea shows that Piringer was not deceived. . . .

The question of contagion *at a distance* (per miasma) was studied in his hospital, where numerous blennorrhoeic patients were placed beside those unaffected, in small wards. He was able to prove definitely that such contagion does not occur and that the cases in which it is suspected can always be traced to direct infection.

The vapor of drying secretion has no power of infection. Even those secretions which are perfectly serous leave a residue when evaporated, and it is this which still retains the contagious properties.

The fluid secretion when kept for three or four days, even without evaporation, is no longer contagious.

If a finger is covered with blennorrhoeic secretion and washed immediately in clear fresh water and well dried, it will cause no infection if rubbed over the conjunctiva.

Blennorrhoeic matter may be smeared over the eyelids if the palpebral fissure is kept firmly closed by adhesive plaster, and no infection will occur. In order to produce infection the secretion must reach the conjunctiva.

The secretion of acute blennorrhea of a moderate degree is just as contagious as that of the most severe. Such pus is capable of producing infection even when diluted with 50 or 100 parts of water. The pus of a very mild purulent ophthalmia and of chronic ophthalmia has much less power of infection.

As long as there is any secretion in any case of purulent ophthalmia, whether mild or severe, so long the case is contagious. When secretion ceases, though there may be considerable congestion and photophobia, the infectious properties are lost.

The properties of infection inherent in the secretion do not vary in different seasons of the year nor under changed atmospheric conditions, whether exposed to the glare of the sun or to the cold of the winter. . . .

Numerous experiments were made to determine the effect upon the contagious properties of the pus when separated for varying intervals of time from the human body. Thus the secretion was collected upon a camel-hair brush and allowed to become as dry as possible ("dry as glass") in from three to six hours. If then applied to the conjunctival sac, but not allowed to soften in the tears, no infection occurred; if softened in the tears, or previously in water, infection was surer to occur.

In seven cases the secretion which had been allowed to dry for thirty-six or forty hours in the open air had lost all contagious property, but in two in which the secretion had been allowed to get dry thirty-three or thirty-four hours in the room and was then softened it produced very severe ophthalmic blennorrhoea.

Pieces of linen smeared with fresh blennorrhoeic matter and given to a pannus patient to wipe his eyes produced infection, but if the cloth had been dried in the air for several days, the patient could use it about the eyes without harm, and the secretion when scraped off the cloth and inserted into the conjunctival sac produced infection only when it was less than thirty-six hours old. On the other hand, if the secretion was placed in a vaccine case and hermetically sealed it retained its contagious property for forty-eight hours, but lost it entirely when kept for three days. The pus from a case of ophthalmia neonatorum produced infection when kept in this way for two and a half days. Piringer therefore concludes that "blennorrhoeic pus loses its contagious properties as it becomes older, and gradually dies in from twenty-six to forty-eight hours, possessing no more organic life when three days have passed." It is upon the discovery of this fact that Piringer bases important rules of prophylaxis, and explains the relative infrequency of gonorrheal ophthalmia among the common people.

The work of Piringer stands out as one of the most carefully conducted series of experiments in the field of medicine before the period of bacteriologic research. It is surprising that his name is not found either in Garrison's or in Castiglioni's medical history.

The question of the contagion of gonorrheal ophthalmia was thus ended. The gonococcus was discovered in 1879. Several years passed before Credé (1819-1892), in 1884, published his prophylaxis of ophthalmia neonatorum,[59] by far the most beneficent contribution of the age to the saving of sight.

In 1857 Pauli[60] read a paper at the first International Ophthalmological Congress, in Brussels, in which he distinguished the two forms under which "Egyptian ophthalmia" had manifested itself: (*a*) the blenorrhagic form, like gonorrheal ophthalmia, and (*b*) granular conjunctivitis, or trachoma. He reported that he had in 1847 produced genital gonorrhea in a man and in a woman by infection with secretion from ophthalmia. In 1854 he repeated the experiment, using the exudate from ophthalmia neonatorum to produce genital gonorrhea in a woman. These experiments seem quite unwarranted after the publication of Piringer's work.

One is surprised to learn that as late as 1864 von Graefe still held to the view that infection might occur not only by contact but also at a distance, the infectious material having been carried by the air.

Among the numberless contributions one must be mentioned especially. There were men like Dalrymple in the middle of the century who condemned the universal practice of venesection in cases of severe ophthalmia, but it was not until 1869 that Soelberg Wells could declare that the practice was wholly abandoned in such cases!

59. Credé, C. S. F.: Die Verhütung der Augenentzündung der Neugeborenen, Berlin, A. Hirschwald, 1884.

60. Pauli, F.: Mémoire sur la nature de l'ophthalmie d'Egypte, Wurzbourg, J. Stahel, 1858.

After this digression, in which I have endeavored to indicate the difficulties which caused long and tedious labor in advancement of knowledge of contagious ophthalmia, I may now return to the general state of ophthalmology. This is clearly seen in the appearance of a number of noteworthy works on diseases of the eye during the first half of the nineteenth century, for example those of Saunders, Travers, Middlemore, Tyrrel and Lawrence, as well as the splendid works of Wardrop and Mackenzie already cited.

Travers in 1821 wrote his well known "Diseases of the Eye":[55]

> In this country, the want of a comprehensive treatise on the diseases of the eye has long been felt and acknowledged. The work of Professor Scarpa was the only book of reference for English students before the publication of Mr. Saunders' treatise . . . on some practical points relating to the eye.

He added:

> In this country, I believe no one before myself, who designed to practice surgery, ventured to give more than a cursory attention to the diseases of the eye. A fear of being disqualified in public opinion, by a reputation acquired in these, for the treatment of other diseases, was a motive, however groundless, sufficient to deter surgeons from the cultivation of a large and legitimate field of observation and practice.

Mackenzie's (1791-1868) "Practical Treatise on the Diseases of the Eye"[56] forms a splendid monument to ophthalmology before the invention of the ophthalmoscope. It appeared first in 1830 and reappeared in several enlarged editions in England and in this country and in translations in France, Germany and Italy. It is a work of great thoroughness and completeness and gives constant evidence of Mackenzie's splendid qualities as an observer and student of disease and of his wide knowledge of the literature. It is today, after more than a century, a most readable book. It is needless for me to mention that Wardrop and Mackenzie were the pioneers in the recognition of sympathetic ophthalmia. Mackenzie made earnest efforts by dissection of glaucomatous eyes to ascertain the changes produced by glaucoma and concluded that "the pressure of the accumulated fluid within the eye is probably the cause of the total blindness which results at last." The condition is often "combined with arthritic inflammation," i. e. acute glaucoma. "Hardness of the Eye is a constant symptom."

Even such meager acquaintance as one forms with the authors in reading the works of Saunders, Travers, Lawrence and Mackenzie suffices to make one appreciate the anecdote that Mackenzie[61] told of the famous Soemmering, whom he heard say that "luckily in England surgery was studied by gentlemen."

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61. Mackenzie, W., by Fischer, I.: British Medicine and the Old Viennese School, Bull. Hist. Med. **11**:174, 1942. Mackenzie visited the Continent in 1815, and he met Soemmering in Munich.

I am now approaching the middle of the nineteenth century and the invention of the ophthalmoscope. The treatise of Mackenzie represents the highest point reached in the path of clinical ophthalmology before this period. It presents a vast advance. It is clear now that this progress was due to the return to the Hippocratic method of careful observation, "the art of trained and accurate observation" (Osler,[1] page 65) and of critical examination. Men may look without seeing, without observing the peculiarities of a clinical picture; "eyes have they, but they see not." It is known that nature is a great magician and that idle gazing does not discover her secrets. It was only when men felt the urge to look more deeply and to understand the conditions and the processes which confronted them that they found the truth.

It is surprising to persons familiar with ocular abnormalities to learn that conditions which appear striking now were so long unrecognized. Thus goiter was described in early times, as was exophthalmos, but more than a thousand years passed before, in 1835, exophthalmic goiter with palpitation was recognized by Graves as a clinical entity!

During this long period clinical ophthalmology relied for its examinations on inspection alone, on unaided vision without any instrumental means in the study of ocular disease. There is but one exception, the use of the magnifying glass. Boerhaave in the early years of the eighteenth century found the magnifying lens helpful in examining the conjunctiva in cases of ophthalmia; Beer used it in the examination of the inflamed iris, and Himly[62] in 1830 described its use for focal illumination "in such cases in which greater illumination is required, as for example to look deeper into the eye or to see the structure of the iris, the course of the blood vessels."

Mackenzie, likewise in 1830, wrote concerning the examination of the crystalline lens in cataract that "with the light concentrated on the pupil by means of a double convex glass, all these particulars are carefully investigated."

It is just half a century ago that Weir Mitchell delivered his memorable address "The Early History of Instrumental Precision in Medicine."[63] Concerning the instruments of precision and precise methods he said:

> The instrument trains the man; it exacts accuracy and teaches care, it creates a wholesome appetite for precision which, at last, becomes habitual. . . . Instruments and methods of precision have so interpreted what we merely see, feel and

62. Himly, K.: Einleitung zur Augenheilkunde, ed. 3, Göttingen, R. Duerlich, 1830. This booklet is the first I have met with which describes the "symptomatic" examination of the eye.

63. Mitchell, S. W.: The Early History of Instrumental Precision in Medicine, New Haven, Conn., Tuttle, Morehouse & Taylor, 1892.

hear, that even though we were again forced to rely upon our unaided senses, we should stand on far higher levels of knowledge than our medical fathers.

Helmholtz presented the ophthalmoscope to the medical world in 1851; forty years later Weir Mitchell was able to state: "A few years ago it was ophthalmology, which in newly acquired precision and in predictive accuracy and therapeutic gain, set up for us more standards of exactness and, enriching our symptomatology, cast light in many directions."

One must restrain oneself in describing the influence which this small instrument has had on medical practice and how it has enlarged the vistas of ophthalmology. That subject alone would require more than one paper. A few facts only must be mentioned. The invention of this instrument was the direct incentive which led, almost immediately, to the development of laryngoscopy and rhinoscopy.

Czermák [64] in his claim of priority to the invention referred specifically to the application of Helmholtz' invention and particularly to the use of the large fixed ophthalmoscopic mirror of Ruete, which he pictured in his first plate. These inventions pointed the way to all the later methods of visual inspection of the accessible internal cavities.

The ophthalmoscope, like the microscope and the telescope, opened up new and wide prospects. The literature of ophthalmology became abundant in publications describing the amazing observations of pathologic processes in the depth of the fundus. Von Graefe and his colleagues and pupils studied and described characteristic fundal pictures. Soon treatises in large number and atlases of colored illustrations appeared: Ruete's in 1854, Liebreich's in 1863 and Jaeger's in 1869.

The fundal picture was found to vary greatly, depending on the primary systemic or organic disease with which it was associated. The intimate relation between fundal pathology and internal medicine grew rapidly in importance to both the clinical ophthalmologist and the general pathologist. Diseases of the central nervous system presented a wide scope of discovery. This fact is brought out most strikingly by the appearance of Allbutt's "On the Use of the Ophthalmoscope in Diseases of the Nervous System and of the Kidneys: also in Certain Other General Disorders" in 1871,[65] of Hughling Jackson's "Remarks on the Routine Use of the Ophthalmoscope in Cerebral Diseases" [66] in 1879

64. Czermák, J. N.: Der Kehlkopfspiegel, Leipzig, Wilhelm Engelmann, 1859; ed. 2, 1863; pp. 26 and 34, pl. 1.

65. Allbutt, T. C.: On the Use of the Ophthalmoscope in Diseases of the Nervous System and of the Kidneys: Also in Certain Other General Disorders, New York, Macmillan & Co., 1871.

66. Jackson, J. H.: Remarks on the Routine Use of the Ophthalmoscope, in Cerebral Disease, M. Press & Circ. **27**:459 and 479, 1879.

and of Gowers' "Manual and Atlas of Medical Ophthalmoscopy" [67] in 1879.

Jackson in an early paper [68] (1863) stated the case clearly:

> I write as a physician, and not as an ophthalmologist. I have studied ophthalmic medicine merely as a help to the study of diseases of the Nervous System. I look at the fundus of the eye, in cerebral cases, when there is even slight failure of sight, in order to ascertain the calibre of the retinal vessels, and the supply of blood to the optic disc, as evidenced by their greater or less coloration.

The intimate relation of fundal changes and diseases of the central nervous system was characteristically expressed in the title under which, in 1876, Bouchut published his "Atlas d'ophthalmoscopie médicale et de cérébroscopie." [69]

The vast literature and the voluminous compilations which have appeared indicate how important ophthalmoscopy has become and what a firm and intimate bond it has woven between ophthalmology and general medicine. This subject has special interest for ophthalmologists because it was Osler who, following the lead of his friend Gowers, made ophthalmoscopic examination of the eye a routine practice. On the other hand, no one did more to urge ophthalmologists to have complete general examinations made of their ophthalmic patients than did George de Schweinitz.

I am not considering here the contributions of de Schweinitz, but mention must be made of his masterly clinical studies of the relation of diseases of the eye to those of the organism, studies which showed the value and the wisdom of complete general examination combined with equally careful examination of the visual organs, and greatly advanced the subject from the point of view of ophthalmologists.

I must pass over the amazing advances made by that genius von Graefe in the short period of his professional life. But there is one outstanding monument to his fame in his discovery of the treatment of acute glaucoma by iridectomy. The increase of ocular tension was known to Galen and to the Arabians. There are a few eighteenth century references to hardness of the eye in glaucoma. Beer described "eyes as hard as flint" and advised noli me tangere, and other investigators made similar observations. Puncture of the eyeball had been practiced. Wardrop had found that increase of the intraocular fluid caused corneal opacity, and he emptied the anterior chamber to relieve it, but von Graefe's idea was a revelation. I have a great personal interest in the

67. Gowers, W. R.: Manual and Atlas of Medical Ophthalmoscopy, London, J. & A. Churchill, 1879.

68. Jackson, J. H.: Observations on Defects of Sight in Brain Disease, and Ophthalmoscopic Examination During Sleep, London, Harrison & Sons, 1863.

69. Bouchut, E.: Atlas d'ophthalmoscopie médicale et de cérébroscopie, Paris, J. B. Baillière et fils, 1876.

following account by my father, Dr. Aaron Friedenwald, dated Jan. 24, 1861, which was published in the *Maryland and Virginia Medical Journal* in April 1861.[70] My father had spent the greater part of the year 1860 in Berlin, and he wrote:

> Among the many great merits which may be claimed for him, [von Graefe] the one outstanding is his satisfactory description of glaucoma, the explanation of its symptoms, and what is more than all, the treatment which he has proposed for it, and successfully practiced. He has proven beyond a doubt that the phenomena which this affection produces, depend on a preternatural intra-ocular pressure. He has called attention to the tense condition of the globe of the eye in support of this view, and has demonstrated with the ophthalmoscope the pulsation of the arteries of the retina, which never becomes sensible to sight under any other condition.

He was under the impression that no account had as yet appeared in English literature.

> Having satisfactorily explained the nature of the disease, Graefe resorted first to the various antiphlogistic remedies, and then to paracentesis of the cornea, but found these inadequate to control it. Having noticed that excision of a piece of the iris, in pursuing other indications, greatly reduced intra-ocular pressure, he tested its efficacy in glaucoma and found it fraught with the happiest results. . . . Graefe is in the prime of life, and devotes himself entirely to the interests of the new science.

Ten years later von Graefe died. His work is a great landmark in the path of clinical ophthalmology.

The effect of the introduction of the ophthalmoscope was undoubtedly enhanced by the three men whose names will ever stand foremost in the development of modern ophthalmology, the stars of first magnitude, von Graefe, Donders and Bowman. Within a few years the entire practice of ophthalmology was lifted to new heights. In every country the great renaissance was seen. It was but six years after the publication of Helmholtz' invention of the ophthalmoscope that the first International Congress of Ophthalmology was held in Brussels, in 1857.

This was an amazing gathering; when one reads the list of names it appears olympic: Mackenzie, Bowman, Critchett, Arlt, Jaeger, Desmarres, Sichel, Donders and von Graefe. It was at this Congress that von Graefe described the curative effect of iridectomy in acute glaucoma. The American delegates were Gross, Squier Littell and Isaac Hays, all of Philadelphia. Gross had been invited to make the report on ophthalmology in America, which more than anything else may make one proud of the progress since made.

Three years after the invention of the ophthalmoscope, Ruete (whose modification of Helmholtz' invention followed so promptly) published

70. Friedenwald, A.: A Letter from Berlin, Maryland & Virginia M. J., April 1861, pp. 349-355.

"Physikalische Untersuchung des Auges." [71] This was the first work devoted to the methods of examination of the eyes, and the only instruments with which it deals are the optometer, two glasses of different colors, the magnifying glass (but not for focal illumination!) and the ophthalmoscope.[72] New instruments of precision, however, followed in rapid succession. Even a partial list is imposing: the perimeter, the phorometer, the ophthalmometer, test types, photometers to measure the light sense, the tonometer, the slit lamp corneal microscope, the camera to photograph the fundus and instruments for the transillumination of the eyeball. One must include roentgen ray examination and application.

But the first effort to secure accuracy of observation was the measurement of central vision and of its improvement by glasses. The older writers, like Bartisch, feared that wearing spectacles was harmful. De St. Ives devoted a chapter to "How to Be Exempted from the Use of Spectacles." A century later, in 1812, Travers did the same.

Fronmueller in 1843 urged that physicians select glasses for their patients, and in the same year Kuechler used print of different-sized type to indicate the clearness of vision; Jaeger in 1854 prepared a more ordered series, and Snellen in 1862 published the standard "Optotypi." [73]

It was not until Donders' [74] work appeared that ophthalmologists recognized the great importance of glasses and applied themselves to their careful selection. Philadelphians may have just pride in the fact that one of the earliest instances of the correction of astigmatism was achieved in their city by Dr. Isaac Hays and that there also, in the well known papers of Weir Mitchell [75] and William Thomson,[76] the importance of correcting errors in refraction was shown in the relief of headaches and other nervous symptoms.

It would be difficult to give an account of the aid which ophthalmology has received from the many departments of clinical medicine

71. Ruete, C. G. T.: Bildliche Darstellung der Krankheiten des menschlichen Auges: Physikalische Untersuchung des Auges, Leipzig, B. G. Teubner, 1854, pts. 1-2.

72. Ruete described and gave a drawing of a small device in which a magnifying glass and a Nicol prism were used to eliminate the annoying light reflex of the cornea.

73. Snellen, H.: Probebuchstaben, zur Bestimmung der Sehschärfe, Utrecht, P. W. van de Weijer, 1862.

74. Donders, F. C.: On the Anomalies of Accommodation and Refraction of the Eyes, translated by W. D. Moore, London, New Sydenham Society, 1864.

75. Mitchell, S. W.: Headaches, from Heat-Strokes, from Fevers, After Meningitis, from Over Use of Brain, from Eye Strain, M. & S. Reporter **31**:67 and 81, 1874; Notes on Headaches, ibid. **32**:101, 1875.

76. Thomson, W.: On Astigmatism as a Cause for Persistent Headache and Other Nervous Symptoms, M. News & Library **37**:81, 1879.

and from the underlying but associated nonclinical branches. There has been no advance in any of these that has not had its bearing on ophthalmology. I might mention, for example, the change that came about when anesthetics were introduced, general and later local; or the boom that Lister's antisepsis wrought; or the fact that Credé's prophylaxis came from an obstetrician.

Much of the advance made in the modern sciences has followed from the discoveries made in sister sciences. Ophthalmology has benefited immeasurably in this manner. I need but call to mind the enormous debt owed to chemistry.

Ophthalmology is deeply indebted to pharmacologists for many alkaloids and other drugs. While the ancients knew the effect of and used the leaves of certain plants (e. g. belladonna) in dilating the pupils, it was not until the last century that the active alkaloids were isolated: atropine and hyoscyamine in the early thirties, pilocarpine in 1875 and homatropine in 1879. Cocaine was isolated in 1855, but it was not until 1884 that Koller discovered its specific qualities and rendered it useful.

Physics has furnished optical inventions and the means of using roentgen rays and radium in examinations and for the treatment of disease.

Bacteriology has provided a basis for the etiologic classification of ophthalmic diseases. With the progress of medicine the relations with biochemistry have been widened and intensified. This science offers great promise of discovery of physiologic and of pathologic processes which are still not understood.

Also, ophthalmology has aided other departments of medical science in no small measure. In the case of general medicine, as has been seen, the relation was one of mutual helpfulness. Modern ophthalmology has been the leader and has offered to the sister branches the incentive in the application of instruments and of methods of precision. I shall mention but one outstanding contribution of ophthalmology to the science of pathology: the monumental work of Leber on inflammation, which was a study of the effect of a vast variety of substances placed into the eyeball.

Some years ago Dr. Welch [77] delivered his magnificent address on the interdependence of medicine with other branches of nature, and he wrote:

> In truth, the boundaries between the divisions and subdivisions of the sciences are being rapidly effaced by a deeper insight into the nature and phenomena of the material universe. . . . An historical sketch . . . of some of the principal phases in the reciprocal relations between medicine and the physical sciences, up to the time when the latter became independent at the close of the 17th century, will show with what propriety medicine has been called the "mother of sciences."

77. Welch, W. H.: The Interdependence of Medicine and Other Sciences of Nature, Science **27**:49, 1908; in Papers and Addresses by William Henry Welch, Baltimore, Johns Hopkins Press, 1920, vol. 3, pp. 315-333.

Huxley had said "Medicine became the foster mother of chemistry."

This interdependence of medicine and the biologic and natural sciences has now become most conspicuously manifest in ophthalmology.

In surveying the course of progress of ophthalmology one observes that it proceeded along a number of paths; at first unrelated, these were gradually brought into communication by connecting trails and later by joining into greatly widened paths. There was long the custom of calling some scientific and others practical. But in method and in purpose the practical have assumed the same spirit as the scientific in the measure of the possible, in the accuracy of observation and in the scrutiny of conclusions. Together they have joined and come into ever closer relation with the natural sciences. Huxley [78] pointed out that "It is a peculiarity of the physical sciences that they are independent in proportion as they are imperfect; and it is only as they advance that the bonds which unite them become apparent." Thus one sees opened the broad avenues of modern science, which are characterized by a unity of endeavor in the search for knowledge and in the service of humanity.

The view that now opens is a wide and limitless expanse; it is the province of medicine, in which each group maintains its own domain but all are bound together by that unity of all medical and surgical practice which characterized ancient Greek medicine, a unity which is now on a vastly higher level.

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78. Huxley, T. H., cited by Garrod, A. E.: The Debt of Science to Medicine, London, Oxford University Press, 1924.

DINITROPHENOL AND ITS RELATION TO FORMATION OF CATARACT

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During the summer of 1935 there occurred a sporadic outbreak of cataracts, predominantly in young women, which could have been likened to an epidemic. It began about April, rapidly increased during the summer and fall and gradually disappeared during 1936-1937. Like an epidemic, it seemed to point to a common source, namely dinitrophenol, which was taken for the rapid reduction of body weight. The number of persons who were affected—estimated at more than 164—probably exceeds the number of cataracts reported in any single toxic epidemic with the possible exception of that due to ergot poisoning. A study of this unusual phenomenon is therefore of interest.

EARLY HISTORY OF DINITROPHENOL

Dinitronaphthol and dinitrophenol were shown to be accelerators of metabolism in dogs by Cazeneuve and Lépine in 1885,[1] by Gibbs and Reichert in 1891 [2] and by later investigators.[3]

Dinitrophenol did not receive medical consideration until the first World War, when it was discovered that many of the explosives manufactured in Europe and in the United States produced toxic effects on the workmen who handled them; these effects varied from malaise to death from poisoning. This discovery led to a series of studies by commissions and committees appointed in the different countries to investigate health hazards in munitions plants. The findings were reported by Magne, Mayer and Plantefol [4] in France, and by Roger Perkins [5] in America, the latter serving as a member of the American National Research Council.

From the Department of Ophthalmology, the University of California Medical School. Candidate's thesis for membership, accepted by the Committee on Theses.

1. Cazeneuve, P., and Lépine, R.: Compt. rend. Acad. d. sc. **101**:1167, 1885.

2. Gibbs, W., and Reichert, E. T.: Am. Chem. J. **13**:289, 1891.

3. Heymans, C., and Bouckaert, J. J.: Arch. internat. de pharmacodyn. et de thérap. **35**:63, 1928. Heymans, C.: J. Pharmacol. & Exper. Therap. **51**:144, 1934.

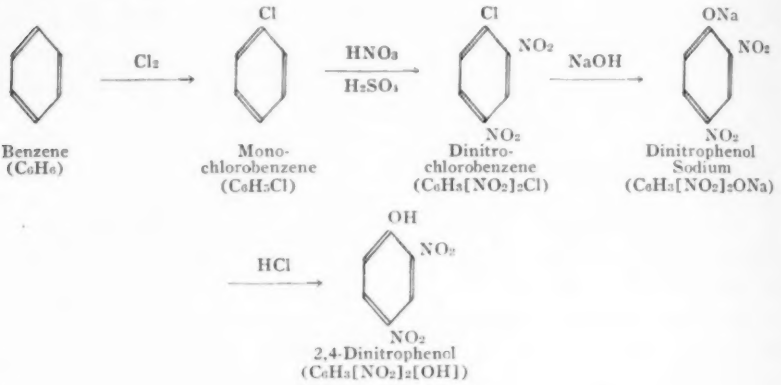
4. Magne, H.; Mayer, A.; Plantefol, L., and others: Ann. de physiol. **7**:269, 1931; **8**:1, 1932.

5. Perkins, R. G.: Pub. Health Rep. **34**:2335, 1919.

Dinitrophenol is particularly a French explosive. In combination with trinitrophenol (picric acid) and trinitrotoluene ("TNT"), it formed most of the filling mixtures used in shells and hand grenades.

CHEMISTRY OF MANUFACTURE

Theoretically dinitrophenol ($C_6H_3(NO_2)_2OH$) is a double nitration of phenol. It is, however, usually made from benzene by the formation of monochlorobenzene. The latter is treated with nitric and with sulfuric acid to form dinitrochlorobenzene. Additional treatment with sodium hydroxide substitutes sodium oxide for the chlorine in the first position, the sodium being removed by the addition of hydrochloric acid, leaving the completed dinitrophenol. These reactions are evident from the accompanying structural formulas.



While there are six possible isomers, all of which are known, the ordinary, or alpha, dinitrophenol is the isomer 1,2,4 with the OH in the first position and the NO_2 groups in the second and the fourth position. Further nitration of dinitrophenol yields trinitrophenol, or picric acid.

The finished dinitrophenol is a yellow solid having a faint odor of phenol. The melting point if the drug is pure is 237 to 238 F. (114 to 115 C.). The solid may be sublimed and carried off in aqueous vapor to the amount of about 2 to 3 Gm. to 2 Kg. of steam at 212 F. (100 C.)—an important point in controlling the health hazards of workers. It is soluble in twenty-one parts of boiling water and in about two hundred and fifty parts of water at 64 F. (18 C.). It is also soluble in alcohol, ether and chloroform. The reaction is definitely acid, and crystalline salts, such as the sodium salt, $C_6H_3(NO_2)_2(ONa)H_2O$, which was the usual form administered in the later treatment of obesity, are readily obtainable.

TOXICITY

The toxicity of dinitrophenol was established by André Mayer (quoted by Perkins [5]), a member of the Conférence pour l'Etude de la Toxicité des Explosits, when he completed a prolonged and elaborate series of experiments on animals and on man in 1918. I quote from a translation of his résumé:

> The long experience of the Service of Explosives in the manipulation of picric acid, of which hundreds of tons have been made and used without serious cases of intoxication, led to the idea that the nitrated phenols are not violent poisons for the human organism. Accordingly, when the manufacture of di-nitro-phenol was begun and the first cases occurred among the workmen, they were put down to impurities in the commercial products. This idea was shown to be incorrect. All the impurities which it was possible to extract, and even all the various compounds of benzene formed in the course of manufacture, were found to be less dangerous than di-nitro-phenol 1-2-4. This, then, is a toxic product, no matter how introduced into the animal organism, whether by ingestion, intravenously, subcutaneously, intraperitoneally, or even rubbed on the skin.

After the recognition of the chief portals of entry (pointed out in the studies of Guerbet and others), quoted by Perkins,[5] consisting of the skin, digestive tract and respiratory tract, the various processes of manufacture, purification and distribution were carefully checked to determine exposure hazards. Preventive measures followed, such as the placing of asbestos curtains about melting vats; use of modified gas masks, ventilators, cuffs above wooden shoes and washable gloves; sanitary eating regulations; rotation of service; medical observation; daily baths, and a change of clothing at the end of the day. The success of these measures is shown in the accompanying table.

Reduction of Deaths Due to the Manufacture of Explosives

Period	Deaths	Tons of Dinitrophenol and Mixture "DD"* Manufactured	Deaths per 10,000 Tons
May 1916 to May 1917	31	19,100	16.3
May 1917 to May 1918	5	40,700	1.2

* A 40-60 mixture of dinitrophenol and trinitrophenol.

Considering the difficulty of enforcing safety regulations among three races, the results are remarkable. The workmen were Frenchmen, Chinese and Annamese and Negro Senegalese, many of whom showed a great abhorrence of water used either externally or internally. Moreover, the workers were either so alarmed by the printed warnings about personal danger that they refused to work and became neurasthenic or, more often, disregarded the warnings completely. Since women were

not employed in dangerous tasks, few were exposed, and hence no cases of illness were reported among them.

EXPERIMENTAL WORK

As the result of the animal experiments of Mayer, previously alluded to, dinitrophenol was proved to be a specific poison. The symptoms emphasized a definite exaggeration of the heat radiation activities, such as thermic polypnea in the dog and vasodilation and sweats in the horse. The body temperature was considerably elevated despite these protective reactions, and in cases of fatal termination the temperature might reach 111 F. (45 C.). Rigor mortis set in immediately after death. The fundamental phenomenon appeared to be an increase of the general oxidation rate of the body. This was observed even in cold-blooded animals and was not affected by nervous stimulation, muscular work or the activity of any particular organ. The glycogen reserves were depleted by the intoxication, and the fat metabolism was believed to be altered. Animals of the same species showed a remarkable variation in susceptibility to the drug, and tolerance to increasing doses was observed in nearly all animals.

POISONING IN MAN

The symptoms of intoxication in man seemed to parallel those observed in animals. The subacute symptoms included gastrointestinal disturbances, such as anorexia, nausea, vomiting, diarrhea and colic. Icterus was rare. Loss of weight, sweats (especially at night), weakness, headaches and dizziness were all recorded. These symptoms might rapidly disappear if the patient remained away from the factory for a few days. As had previously been observed in animals, susceptibility varied widely, since only a limited number of persons were affected, even under the worst working conditions. Alcoholism, lesions of the liver and kidneys and a general lessened resistance among the workers made them poor risks.

Urinalysis proved of definite clinical value in determining the cases of serious poisoning. Although unchanged dinitrophenol and various reduction products might be found in subjects displaying no clinical signs of intoxication, amino-2-nitro-4-phenol was always found in abundance in persons seriously poisoned. This fact was made the basis of a specific test of urine, known as Derrien's test.[6] This test involved an azo reaction, a positive reaction being violet, wine color or orange-red, whereas a negative reaction was either colorless or yellow. A positive Derrien

6. (*a*) Bolliger, A.: M. J. Australia **1**:367, 1934. (*b*) Anderson, H. H.; Reed, A. C., and Emerson, G. A.: Toxicity of Alpha-Dinitrophenol: Report of a Case, J. A. M. A. **101**:1053 (Sept. 30) 1933. (*c*) Perkins.[5]

reaction which became increasingly high or remained high indicated impending acute intoxication. Positive Derrien reactions were later used to indicate neglect in the enforcement of preventive measures in a particular factory.

Acute poisoning usually followed as a sequel to subacute symptoms. The onset was sudden, with complaints of tiredness in the legs and arms, painful constrictions at the base of the chest and a burning thirst. Pallor, cyanosis, profuse sweating, agitation and dyspnea occurred, together with a moderate elevation of the temperature. The urine diminished in amount, and the Derrien reaction became increasingly positive. Prompt removal from work and rest usually brought relief. The patient remained off duty until the urine became normal, with a minimum rest period of eight days. Fulminating intoxication was most marked among alcohol addicts and persons with renal or hepatic diseases. With such intoxication death might supervene within a few hours. The patient suddenly found that he was unable to work, or he collapsed on the way home. He was seized with colic and diarrhea. The temperature rose to 104 F. (40 C.) or higher, sweating was profuse and the skin was stained yellow. Thirst was intense. The heart beats remained regular, and the lungs exhibited only occasional scattered rales. The patient became frightened and excited, and general or partial convulsions appeared. Unconsciousness, coma and death followed in a few hours, the death resembling that occurring in uremic poisoning. Rigor mortis set in immediately, a conspicuous feature previously mentioned in connection with experimental animals. This phenomenon was believed to be due to the extreme dehydration.

At postmortem examination no characteristic lesions were found. The acute edema of the lungs mentioned was believed to be secondary to toxic effects on the vasomotor system. Microscopic lesions of the liver and kidney cells were inconstant, and typical changes were lacking elsewhere. The presence of dinitrophenol within the body was not characteristic, since the poison was also found in the bodies of workmen who had died from accidental causes. It is to be noted in passing that in all the studies reported only 1 workman complained of poor vision. This man was working in a dinitrotoluene plant, and it is possible that he had an ocular defect that was unrelated to the intoxication.

In 1928 Prof. C. Heymans, of Ghent,[3] and others [7] revived interest in the fever-producing and other properties of nitrated naphthols. Their researches stimulated Tainter and his co-workers to study alpha dinitrophenol.

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7. (*a*) Koelsch, F.: Zentralbl. f. Gewerbehyg. u. Unfallverh. **4**:261, 1927. (*b*) Leyman: Concordia, Berlin **9**:55, 1928. Cited by Anderson, Reed and Emerson.[6b]

INVESTIGATIONS IN AMERICA

In 1931 Tainter and Cutting and their associates [8] began an elaborate series of independent studies on the pharmacology of dinitrophenol. They confirmed much of the work cited in the French and Belgian reports and made additional investigations as to certain possible clinical uses of the drug.[9]

Proved experiments showed that dinitrophenol was able to increase the consumption of oxygen in animals to as much as twelve times the normal amount.[10] The increased metabolism was noticeable within one minute after the injection and varied with the size of the dose, which could be raised to a point at which the animal died from the excessive heat production. The increase in metabolism was peripheral and was due to direct stimulation of the cellular metabolism. The metabolic response was not prevented by destruction or curarization of brain or cord or by removal of the thyroid or the adrenal glands. Heightened oxidation was accompanied by a marked increase in the respiratory rate, which was probably due to a greater oxygen demand and to an increased carbon dioxide production. The pulse rate and the blood pressure were not raised so long as the circulatory and the respiratory system kept pace with the increased oxidation and neither anoxemia nor acidosis developed. The drug decreased the supply of glycogen in the liver and muscles, raised the blood sugar content and increased the lactic acid content of the blood and muscles. The increased metabolism was primarily at the expense of fats and carbo-

8. (*a*) Cutting, W. C., and Tainter, M. L.: Proc. Soc. Exper. Biol. & Med. **29**:1268, 1932. (*b*) Tainter, M. L.; Boyes, J. H., and DeEds, F.: Arch. internat. de pharmacodyn. et de thérap. **45**:235, 1933. (*c*) Tainter, M. L., and Cutting, W. C.: J. Pharmacol. & Exper. Therap. **48**:410, 1933; (*d*) **49**:187, 1933. (*e*) Cutting, W. C., and Tainter, M. L.: Metabolic Actions of Dinitrophenol with Use of Balanced and Unbalanced Diets, J. A. M. A. **101**:2099 (Dec. 30) 1933; (*f*) Proc. Soc. Exper. Biol. & Med. **31**:97, 1933. (*g*) Tainter, M. L.: ibid. **31**:1161, 1934. (*h*) Cutting, W. C.; Rytand, D. A., and Tainter, M. L.: J. Clin. Investigation **13**:547, 1934. (*i*) Cutting, W. C.; Mehrtens, H. G., and Tainter, M. L.: Actions and Uses of Dinitrophenol: Promising Metabolic Applications, J. A. M. A. **101**:193 (July 15) 1933. (*j*) Tainter, M. L.; Stockton, A. B., and Cutting, W. C.: Use of Dinitrophenol in Obesity and Related Conditions: Progress Report, ibid. **101**:1472 (Nov. 4) 1933. (*k*) Stockton, A. B., and Cutting, W. C.: Clinical Circulatory Effects of Dinitrophenol, ibid. **103**:912 (Sept. 22) 1934. (*l*) Tainter, M. L.; Cutting, W. C., and Stockton, A. B.: Am. J. Pub. Health **24**:1045, 1934. (*m*) Tainter, M. L.; Cutting, W. C., and Hines, E.: J. Pharmacol. & Exper. Therap. **55**:326, 1935. (*n*) Tainter, M. L.; Stockton, A. B., and Cutting, W. C.: Dinitrophenol in Treatment of Obesity: Final Report, J. A. M. A. **105**:332 (Aug. 3) 1935.

9. Cutting and Tainter.[8a] Cutting, Mehrtens and Tainter.[8i]

10. Hall, V. E.; Field, J., II; Sahyun, M., and others: Am. J. Physiol. **106**: 432, 1933.

hydrates. Experimental animals acquired tolerance to the drug only when exceedingly high doses were given. The fatal dose for various species was determined at 20 to 30 mg. per kilogram of body weight. No specific antidote was found. In experimental animals death resulted from direct circulatory depression, high fever, acidosis and anoxemia. Tainter and Cutting were unable to find any significant damage to important organs of dogs given daily just short of fatal doses of dinitrophenol for periods of six months.

EFFECTS IN MAN

In human beings the action of dinitrophenol agreed closely with that observed in animals given equivalent doses. In July 1933 Cutting, Mehrtens and Tainter [8] reported that 9 patients had been given from 3 to 5 mg. of the drug daily for periods of from one to ten weeks. For 6 of these the metabolic rate was repeatedly determined and was found to be maintained at an average of 40 per cent above normal. All the subjects lost weight without dietary restrictions. Changes in temperature, pulse rate and respiration were not observed, although the amount of perspiration was increased. No undesirable symptoms were encountered, and the patients stated that they felt better and were more active than before taking the drug. These authors stated the belief that preliminary results in patients indicated that dinitrophenol could satisfactorily increase metabolism, experimentally and therapeutically, and might "be useful in the treatment of obesity, hypothyroidism and similar depressed metabolic states."

Anticipating extended clinical application of the drug, the authors carefully pointed out the dangers that might arise therefrom. They emphasized the point that the drug had been continuously administered to animals and to man for no more than three months and only to normal subjects. They had no assurance that toxic manifestations might not appear after more prolonged dosage or in diseased persons. They pointed out that excessive doses could cause fatal hyperpyrexia and warned against possible idiosyncrasies, such as unusual sensitivity or an atypical response to the drug. They recommended that "dinitrophenol be used only as an experimental therapeutic procedure in carefully selected patients under close observation by the physician." This warning was repeated both as an editorial [11] in the same issue of *The Journal of the American Medical Association* and in a preliminary report of the Council on Pharmacy and Chemistry.[12]

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11. Dinitrophenol: A Metabolic Stimulant, editorial, J. A. M. A. **101**:213 (July 15) 1933.

12. Alpha-Dinitrophenol, Preliminary Report of the Council on Pharmacy and Chemistry, J. A. M. A. **101**:210 (July 15) 1933.

In November 1933 Tainter, Stockton and Cutting [8j] published a progress report covering 113 consecutive, unselected cases of obesity treated by dinitrophenol. Of the patients, 98 were female and 15 male. About one half had previously received thyroid and had undergone dietary regimens until no further weight loss was effected; hence they represented the more unresponsive types of obesity.

The treatment was successful in 101 (89.4 per cent) cases. An average loss of weight of between 2 and 3 pounds (0.9 and 1.3 Kg.) a week was obtained by an average daily dose of 0.3 Gm. The loss was shown by measurements to be predominantly from the hips and abdomen. Those patients who were not on special diets at the beginning of the treatment were allowed to eat their regular fare without restrictions.

Persons who had taken the drug continuously for four months showed no demonstrable evidence of cumulative or toxic effects. Certain side actions were observed in others; these will be mentioned farther on. Administration of the drug was stopped in 3 cases because of unsatisfactory weight loss with average doses and in 9 others because of undesirable reactions. The initial dose for adults was fixed at 100 mg. of the sodium salt (equivalent to 75 mg. of dinitrophenol) given in capsules daily with meals. This dose was to be increased at weekly intervals as necessary to a point at which 2 to 3 pounds of body weight were lost a week or until symptoms of warmth and sweating became unpleasant. The danger of indiscriminate or careless overdosing was again stressed.

During 1933 Dodds and Robertson [13] published three communications dealing with the clinical application of a related nitro compound, 4,6-dinitroorthocresol. They claimed that this drug was from three to five times as powerful as dinitrophenol although its toxicity was no greater. They stated the belief that dinitroorthocresol was superior for weight reduction, since equal effects could be secured with one-third the dose. These observers defined a safe dose as 50 to 100 mg. a day, or 0.5 to 1 mg. per kilogram of body weight. They said that the effect of the drug used therapeutically was best determined by making measurements of the basal metabolic rate and that discomfort or toxic symptoms did not occur when the basal rate was maintained between + 30 and + 50. They considered any rate above + 50 dangerous. Experiments convinced these authors that metabolic stimulants of the dinitro group were of no use in alleviating myxedema, a potentiality that had been suggested by Tainter.[8j] Dinitroorthocresol and mixtures containing this drug were used extensively in Europe in "reducing cures."

13. Dodds, E. C., and Pope, W. J.: Lancet **2**:352, 1933. Dodds, E. C., and Robertson, J. D.: ibid. **2**:1137 and 1197, 1933.

POPULARITY OF DINITROPHENOL TREATMENT

The popular response to dinitrophenol was immediate and overwhelming. The drug appealed to the imagination of both physician and patient. Here was a drug that would apparently banish the tired feeling that accompanied low metabolic states without inducing the deleterious symptoms that might result from equivalent doses of thyroid extract. Corpulent females could lose unwanted poundage without the necessity or inconvenience of dietary restrictions! In spite of repeated warnings,[14] dinitrophenol was used to an astounding degree in the treatment of obesity. It is estimated that during the first fifteen months following its introduction [81] 100,000 persons took the drug for weight reduction. More than 1,200,000 capsules of 0.1 Gm. each were dispensed from a single clinic in San Francisco. This figure would correspond to about 4,500 patients. More than twenty drug houses offered to supply both dinitrophenol and mixtures containing the drug. Many of these remedies could be procured without prescription and with no further directions than to take "1 capsule three times daily after meals."

TOXIC EFFECTS

It is not surprising that under the circumstances instances of toxic reactions began to appear in the literature. Gastrointestinal symptoms, consisting of nausea, vomiting and loss of appetite, were common. Cutaneous lesions, however, were the most frequent, with an incidence of from 8 to 23 per cent.[15] These lesions included maculopapular dermatitis, urticaria and angioneurotic-like swelling, accompanied by itching and burning. Although the majority of lesions were mild, others were severe. The lesions in Hitch and Schwartz's case [15f] per-

14. Quick, A. J.: Dangerous Drug Reactions, Correspondence, J. A. M. A. **102**:1419 (April 28) 1934. Dinitrophenol in Obesity, editorial, ibid. **103**:1950 (Dec. 22) 1934. Toxicity of Dinitrophenol, Current Comment, ibid. **101**:1080 (Sept. 30) 1933.

15. (*a*) Hirsch, S.: Report of a Toxic Manifestation Due to "Dinitrenal," correspondence, J. A. M. A. **102**:950 (March 24) 1934. (*b*) Frumess, G. M.: Allergic Reaction to Dinitrophenol: Report of Case, ibid. **102**:1219 (April 14) 1934. (*c*) Jackson, H., and Duvall, A. I.: Dinitrophenol Poisoning: Report of Case, ibid. **102**:1844 (June 2) 1934. (*d*) Matzger, E.: Can Sensitivity to Dinitrophenol Be Determined by Skin Tests? ibid. **103**:253 (July 28) 1934. (*e*) Noun, M. H.: Urticaria, Edema and Purpura Following Small Doses of Di-Nitrophenol: Report of a Case, Arch. Dermat. & Syph. **32**:288 (Aug.) 1935. (*f*) Hitch, J. M., and Schwartz, W. F.: Late Toxic Results, Including Dermatitis Exfoliativa, from "Slim" (Dinitrophenol), J. A. M. A. **106**:2130 (June 20) 1936. (*g*) Simkins, S.: Dinitrophenol and Desiccated Thyroid in Treatment of Obesity, ibid. **108**:2110 (June 19); 2193 (June 26) 1937. (*h*) Anderson, Reed and Emerson.[6b] (*i*) Tainter, Stockton and Cutting.[8j]

sisted for over ten months and were complicated by polyneuritis, otitis media and cataract. One case of alopecia was reported.[15g] Cutaneous tests were of no value in indicating individual hypersensitivity.[16]

Aural Complications.—Dintenfass [17] and Hitch and Schwartz [15f] reported exudative otitis media in 2 patients.

Agranulocytosis.—In view of the similarity of dinitrophenol to benzene, changes in the bone marrow might have been anticipated. Eight cases of agranulocytosis were reported, with 3 fatalities.[18] The smallest amount of the drug taken in these cases was 5.6 Gm. over a period of fourteen days. In the other cases the average was 12 Gm. over fifty-eight days.

Neuritis.—Under this head are included aberrations of taste (loss for salt and sweet) and multiple regional involvement affecting particularly the feet and legs. Thirty cases were reported in the literature.[19] Symptoms appeared after an average of ten weeks, followed ordinary therapeutic doses and persisted for weeks or months.

Complications Involving the Cardiovascular System.—Remarkably few changes in the cardiovascular system were reported. Electrocardiographic evidence of functional damage was offered by MacBryde and Taussig [20] and by de Châtel and Motika.[19c] Poole and Haining [21] and

16. Frumess.[15b] Matzger.[15d]

17. Dintenfass, H.: Ear Complication from Dinitrophenol Medication, J. A. M. A. **102**:838 (March 17) 1934.

18. (*a*) Hoffman, A. M.; Butt, E. M., and Hickey, N. G.: Neutropenia Following Amidopyrine: Preliminary Report, J. A. M. A. **102**:1213 (April 14) 1934. (*b*) Bohn, S. S.: Agranulocytic Angina Following Ingestion of Dinitrophenol, ibid. **103**:249 (July 28) 1934. (*c*) Davidson, E. N., and Shapiro, M.: Neutropenia Following Dinitrophenol, with Improvement After Pentnucleotide and Leukocyte Cream, ibid. **103**:480 (Aug. 18) 1934. (*d*) Silver, S.: New Danger in Dinitrophenol Therapy: Agranulocytosis with Fatal Outcome, ibid. **103**:1058 (Oct. 6) 1934. (*e*) Imerman, S. W., and Imerman, C. P.: Dinitrophenol Poisoning, with Thrombocytopenia, Granulopenia, Anemia and Purpura Complicated by Lung Abscess, ibid. **106**:1085 (March 28) 1936. (*f*) Dameshek, W., and Gargill, S. L.: New England J. Med. **211**:440, 1934.

19. (*a*) Nadler, J. E.: Peripheral Neuritis Caused by Prolonged Use of Dinitrophenol, J. A. M. A. **105**:12 (July 6) 1935. (*b*) Epstein, E., and Rosenblum, H.: J. Lab. & Clin. Med. **20**:1118, 1935. (*c*) de Châtel, A., and Motika, J.: Deutsches Arch. f. klin. Med. **176**:700, 1934. (*d*) Cogan, D. G., and Cogan, F. C.: New England J. Med. **213**:854, 1935. (*e*) Tainter, Stockton and Cutting.[8j] (*f*) Anderson, Reed and Emerson.[6b]

20. MacBryde, C. M., and Taussig, B. L.: Functional Changes in Liver, Heart and Muscles and Loss of Dextrose Tolerance Due to Dinitrophenol, J. A. M. A. **105**:13 (July 6) 1935.

21. Poole, F. E., and Haining, R. B.: Sudden Death from Dinitrophenol Poisoning: Report of Case with Autopsy, J. A. M. A. **102**:1141 (April 7) 1934.

Tainter and Wood [22] reported finding fragmentation of the heart muscle at autopsy in fatal cases. Tachycardia and a fall in blood pressure were occasionally noted. Hypertensive patients showed a definite lowering of both systolic and diastolic pressure, but hypotensive patients exhibited little change.[23]

Effects on Hepatic Function.—Jaundice and other symptoms of damage to the liver were reported by various observers.[24] Graham [25] has demonstrated that the liver is less able to withstand toxic substances when the glycogen content is low. Some investigators believe that this may be a factor in toxic reactions to dinitrophenol. Simkins,[15g] however, in a late analysis, concluded that in therapeutic doses the drug is rarely injurious to the liver. This conclusion agrees with the findings of Koch, Lee and Tainter [26] and Schulte.[27]

Effects on Renal Function.—Although instances of damage to the kidneys have been reported,[28] most observers believe that this rarely occurs.

MORTALITY

A total of 9 deaths have been reported from the use of dinitrophenol and 1 from dinitroorthocresol.[29] Three patients died from overdoses. Three of the remainder had agranulocytosis. In the majority of cases death occurred within twenty-four hours after the onset of such toxic manifestations as dizziness, fatigue, dyspnea, high temperature, intense

22. Tainter, M. L., and Wood, D. A.: Case of Fatal Dinitrophenol Poisoning, J. A. M. A. **102**:1147 (April 7) 1934.

23. Stockton and Cutting.[8k] Simkins.[15g]

24. (*a*) Haft, H. H.: Toxicity of Dinitrophenol, Correspondence, J. A. M. A. **101**:1171 (Oct. 7) 1933. (*b*) Sidel, N.: Dinitrophenol Poisoning Causing Jaundice: Report of Case, J. A. M. A. **103**:254 (July 28) 1934. (*c*) Warthin, A. S.: Bull. Internat. A. M. Museums **7**:123, 1918. (*d*) Onfray, R., and Gilbert-Dreyfus: Bull. Soc. franç. d'opht. **50**:114, 1937. (*e*) Koelsch.[7a] (*f*) MacBryde and Taussig.[20] (*g*) Poole and Haining.[21]

25. Graham, E. A.: J. Exper. Med. **21**:185, 1915.

26. Koch, R. A.; Lee, R. C. H., and Tainter, M. L.: California & West. Med. **43**:337, 1935.

27. Schulte, T. L.: J. Pharmacol. & Exper. Therap. **59**:419, 1937.

28. Rabinowitch, I. M., and Fowler, A. F.: Canad. M. A. J. **30**:128, 1934. Poole and Haining.[21] Tainter and Wood.[22] Koelsch.[7a]

29. Goldman, A., and Haber, M.: Acute Complete Granulopenia with Death Due to Dinitrophenol Poisoning, J. A. M. A. **107**:2115 (Dec. 26) 1936. Masserman, J. H., and Goldsmith, H.: Dinitrophenol: Its Therapeutic and Toxic Actions in Certain Types of Psychobiologic Underactivity, ibid. **102**:523 (Feb. 17) 1934. Death After Slimming Treatment, Lancet **1**:489, 1934. Lattimore, J. L.: J. Kansas M. Soc. **35**:388, 1934. Leutsker, R. J.: U. S. Nav. M. Bull. **33**:394, 1935. Purvine, R.: Fatal Poisoning from Sodium Dinitrophenol, J. A. M. A. **107**:2046 (Dec. 19) 1936. Poole and Haining.[21] Tainter and Wood.[22]

thirst and excessive perspiration. As had been observed in animals, rigor mortis set in immediately after death.

SUCCESSFUL WEIGHT REDUCTION

Interim studies had confirmed the potency of dinitrophenol as a slimming agent. Tainter, Stockton and Cutting [8n] obtained weight reduction in 165 of 170 unselected cases (97 per cent). In a review of 290 cases in the literature, McGavack [30] showed a weight loss in 276 (95 per cent). Simkins,[15g] in his comprehensive clinical study of 181 unselected cases of obesity, recorded a lower figure (79.7 per cent) for 59 cases. He found that the effectiveness of dinitrophenol as a reducing agent could be increased substantially by the addition of desiccated thyroid.

The amount of weight lost by patients receiving dinitrophenol varied. Nineteen patients reported on by Whalman [31] lost an average of 37.7 pounds (17 Kg.) apiece. Simkins [15g] obtained only 11.1 pounds (5 Kg.) of average loss in 47 cases. Individual results varied from no loss to a loss of 140 pounds (63.5 Kg.) in one series.[15g] Some reports (Strang and Evans [32]) questioned the practical value of dinitrophenol in reducing weight, but proportionately few negative results are mentioned in the literature.

On July 6, 1933 the Council on Pharmacy and Chemistry of the American Medical Association recommended that dinitrophenol not be accepted for inclusion in "New and Nonofficial Remedies." [33] In arriving at this recommendation the Council pointed out that dinitrophenol as a new drug should await further study in laboratories and clinics before being put into general use as a remedy for obesity. It stated further that "to treat a mild chronic condition such as obesity with a toxic agent capable of inducing serious injury and death appears to be unjustified." The Council recommended that restrictions be placed on the sale of the drug and that its use be limited to selected patients and be supervised by properly trained physicians. The dangers of dinitrophenol had already received official recognition in Germany,[34] Canada [35] and England.[36] The most drastic legal regulation of dinitrophenol to date has been

30. McGavack, T. H.: California & West. Med. **44**:77, 1936.

31. Whalman, H. F.: Am. J. Ophth. **19**:885, 1936.

32. Strang, J. M., and Evans, F. A.: Evaluation of Dinitrophenol as Aid in Weight Reduction, J. A. M. A. **104**:1957 (June 1) 1935.

33. Dinitrophenol Not Acceptable for N. N. R., Report of the Council on Pharmacy and Chemistry, J. A. M. A. **105**:31 (July 6) 1935.

34. Reichsgsndhts.-Bl. **9**:1078, 1934.

35. Bar Sale of Dinitrophenol, Medical News (Canada), J. A. M. A. **103**:1243 (Oct. 20) 1934.

36. Dekrysil Treatment: The Paddington Inquest, Special Articles, Lancet **1**: 652, 1934. Dinitrophenol Compounds in Obesity, editorial, ibid. **1**:746, 1934.

enacted in California [37] (California Laws, 1939, C582). This makes it a felony for any person to sell, dispense, administer or prescribe dinitrophenol for human consumption. In order to procure the drug a prescription is obligatory in Connecticut, Florida, Nevada, North Carolina and other states.

CATARACTS

The development of cataracts following dinitrophenol therapy was first described by Horner, Jones and Boardman,[38] in July 1935. In this communication we reported 3 cases of bilateral incipient cataract occurring in women who had taken considerable quantities of the drug for weight reduction. One of us (Jones) had made careful medical records of these patients and the data obtained, together with the fact that the average age was 38 years, made the development of cataracts from any other cause appear unlikely. All 3 patients showed similar powdery anterior subcapsular changes, denser posterior subcapsular opacities resembling brass filings and rapid loss of vision. In other articles Boardman [39] reviewed 2 of these cases and mentioned 8 others that had come to his attention. In each report the point that the use of dinitrophenol should be stopped pending further study was stressed.

During the next two months, 7 additional writers reported cases.[40] In October 1935 Cogan and Cogan [19d] reviewed the first 20 cases that had appeared in the literature. Other reports followed.[41] Rodin [41d]

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37. Diphenylamine, Organization Section, J. A. M. A. **114**:880 (March 9) 1940.

38. Horner, W. D.; Jones, R. B., and Boardman, W. W.: Cataracts Following Use of Dinitrophenol: Preliminary Report of Three Cases, J. A. M. A. **105**:108 (July 13) 1935.

39. Boardman, W. W.: California & West. Med. **43**:118, 1936; Ann. Int. Med. **9**:195, 1935.

40. (*a*) Shutes, M. H.: Am. J. Ophth. **18**:752, 1935. (*b*) Josephson, E. M.: Science **82**:222, 1935. (*c*) Kniskern, P. W.: Cataracts Following Dinitrophenol, J. A. M. A. **105**:794 (Sept. 7) 1935. (*d*) Cogan, D. G., and Cogan, F. C.: Dinitrophenol Cataract, ibid. **105**:793 (Sept. 7) 1935. (*e*) Lazar, N. K.: Cataract Following Use of Dinitrophenol, ibid. **105**:794 (Sept. 7) 1935. (*f*) Allen, T. D., and Benson, V. M.: Late Development of Cataract Following Use of Dinitrophenol About a Year Before, ibid. **105**:795 (Sept. 7) 1935. (*g*) Glowacki, B. F.: J. Michigan M. Soc. **34**:535, 1935.

41. (*a*) Rundles, W. Z.: J. Michigan M. Soc. **34**:777, 1935. (*b*) Mann, W. A., Jr.: Cataract Due to Di-Nitrophenol, Arch. Ophth. **15**:116 (Jan.) 1936. (*c*) Hill, H. E.: J. Indiana M. A. **29**:67, 1936. (*d*) Rodin, F. H.: California & West. Med. **44**:276, 1936. (*e*) Spaeth, E. B.: Am. J. Ophth. **19**:320, 1936. (*f*) Veasey, C. A.: ibid. **19**:332, 1936. (*g*) Barkan, H.; Borley, W. E.; Fine, M., and Bettman, J.: California & West. Med. **44**:360, 1936. (*h*) Mengel, W. G.: Am. J. Ophth. **19**:512, 1936. (*i*) Lehrfeld, L.: ibid. **19**:513, 1936. (*j*) Differential Diagnosis of Cataract Due to Dinitrophenol, Queries and Minor Notes, J. A. M. A. **107**:60 (July 4) 1936. (*k*) Loomis, E. A.: Am. J. Ophth. **19**:515, 1936. (*l*)

(Footnote continued on next page)

reviewed 32 cases, particularly as to age, duration of treatment and onset of lenticular changes. Whalman,[31] in October 1936, in an excellent paper, tabulated 27 cases and in an appended note stated that since completing his paper his list of cases had been increased to 40. This is the largest series in the literature. Although a majority of the cataracts due to the drug have occurred in California, cases from nearly all sections of the country are on record.

EUROPEAN CASES

Vannas,[42] in Finland, in December 1935 reported the first "dinitro cataract" in Europe. This cataract followed the use of dinitroorthocresol [13] as a "reducing cure" and is the first cataract on record due to this drug. Vannas was the first author to make a histologic study of cataract from this cause. Other cases were reported from the Netherlands (van der Hoeve and Daniels [43]), from Finland (Helminen [44] and Lindberg [45]), from Switzerland (Vogt [46]), from France (Onfray and Gilbert-Dreyfus [24d] and Sedan [47]), from Brazil (Oneto, Gallino and Natale [48]), from Italy (Ciotola [49]), from Sweden (Ploman [50]) and from Denmark (Mählén [51]).

Rank, R. T., and Waldeck, E. A.: Wisconsin M. J. **35**:629, 1936. (*m*) Horner, W. D.: Cataract Following Di-Nitrophenol Treatment for Obesity, Arch. Ophth. **16**:447 (Sept.) 1936. (*n*) Frost, A. D., in discussion on Horner. (*o*) Whedon, E., in discussion on Horner. (*p*) Swett, W. F.: Am. J. Ophth. **19**:796, 1936. (*q*) Davis, W. T.: M. Ann. District of Columbia **6**:246, 1937. (*r*) McDannald, C.: Cataract Due to Dinitrophenol, Arch. Ophth. **17**:944 (May) 1937. (*s*) Hessing, E. E.: Cataract Due to Dinitrophenol, ibid. **17**:513 (March) 1937. (*t*) Welton, C. B.: Illinois M. J. **73**:72, 1938. (*u*) Weight Controls: Cataracts Develop Following Use of Anti-Fat Nostrum, Report of the Bureau of Investigation, J. A. M. A. **111**:188 (July 9) 1938. (*v*) Lewis, A. C.: Am. J. Ophth. **21**:788, 1938. (*w*) Whalman.[31]

42. Vennas, M.: Acta Soc. med. fenn. duodecim (Ser. B, fasc. 2, art. 4) **22**: 1, 1936; abstracted, Zentralbl. f. d. ges. Ophth. **38**:516, 1937.

43. van der Hoeve, J., and Daniels, A. P.: Nederl. tijdschr. v. geneesk. **80**:126, 1936. Cataract and Dinitrophenol, Foreign Letters (Netherlands), J. A. M. A. **107**: 1237 (Oct. 10) 1936.

44. Helminen, T.: Acta ophth. **15**:490, 1937.

45. Lindberg, J. G.: Acta ophth. **16**:556, 1938.

46. Vogt, A.: (*a*) Schweiz. med. Wchnschr. **67**:873, 1937; (*b*) Klin. Monatsbl. f. Augenh. **99**:669, 1937.

47. Sedan, J.: Ann. d'ocul. **176**:191, 1939.

48. Oneto, J. A.; Gallino, J. A., and Natale, A.: Arch. de oftal. de Buenos Aires **12**:731, 1937; abstracted, Am. J. Ophth. **21**:476, 1938.

49. Ciotola, G.: Boll. d'ocul. **16**:531, 1937.

50. Ploman, K. G.: Hygiea **99**:688, 1937; abstracted, Zentralbl. f. d. ges. Ophth. **41**:691, 1938.

51. Mählén, S.: Acta ophth. **16**:563, 1938.

RÉSUMÉ OF CASES

From these case reports it became apparent that dinitrophenol cataracts presented certain new and characteristic features:

1. They occurred in young women who were physically normal save for varying degrees of obesity and who were in an age group in which senile cataracts do not occur. 2. They were bilateral and appeared either during or after periods of slimming treatment with dinitro bodies. 3. An interval of months or years might elapse between the time the last dose was taken and the onset of blurred vision. 4. The lenticular changes were strikingly similar and could be demonstrated with the biomicroscope at a time when vision for distance and for reading was still normal. 5. After a gradual onset, the lenticular changes progressed with startling rapidity until the vision was obscured. 6. Treatment was without effect in staying their progress. 7. Surgical extraction of the lens was uniformly successful in restoring vision.

Lenticular Changes.—The earliest lenticular changes consisted of faint gray, striated, powdery, downy or lacelike opacities situated just beneath the anterior capsule. The capsule remained transparent, but was often described as appearing "dry" or "pebbly" because of the presence of water vacuoles beneath it. The cortex was either clear or contained small, whitish, discrete, corn-meal-like granules. The nucleus was unaffected. The most spectacular change, however, occurred in the posterior part of the lens. Here, in the subcapsular region, was a dense, saucer-shaped, granular deposit with a golden, sometimes silvery, luster. This deposit resembled brass filings, cloth of gold, hammered copper or silvery or polychromatic crystals. The adjoining vitreous was normal. The cornea, aqueous, iris and fundus were normal. Certain exceptions were observed. An aqueous flare was mentioned by Cogan and Cogan [40d] and Whalman.[31] Fine, dustlike opacities were described on the posterior part of the cornea by Allen and Benson [40f] and on the lens by Oneto and others.[48] McDannald [41r] observed scattered areas of atrophy in the pigmented layer of the uvea in both the eye operated on and the eye not operated on in 1 case. Swett [41p] described a case of conjunctival slough and symblepharon which accompanied an extensive desquamative dermatitis and involvement of the mucous membrane. Ultimately one eye was lost. Frost [41n] reported 1 case of partial, secondary optic nerve atrophy with final vision of 20/50, field defects and pale disks.

Visual impairment during the early stages was slight and might be improved by glasses. The patients showed a characteristic increase in hyperopia. After an interval of weeks the vision suddenly and rapidly grew worse. The opacities became intumescent and invaded the cortex and finally the nucleus, so that the whole lens grew opalescent and silky

gray or pearly, sometimes with the speed of development of a traumatic cataract. Lamellar dissolution [45] and fine striation were also described.

The late stages were characterized by varying disintegration of the whole lens into sector-like fragments separated by dark, intervening, spokelike bands. The lens swelled early in the process, the anterior chamber became shallow and the tension increased, occasionally to the stage of acute secondary glaucoma. Helminen [44] encountered 4 such cases, Hessing [41s] 3, Horner [41m] 4 and Whalman [31] 2, and other cases are mentioned in the literature. Welton [41t] observed an unfortunate patient in whom bilateral cataract, glaucoma, panophthalmitis and phthisis bulbi developed. A patient living in the vicinity of San Francisco lost her vision from a similar secondary glaucoma.

The increase of hyperopia, often 2 or 3 D., previously mentioned, is remarkable, since it is the opposite of the usual manifestation of a swollen lens. As the lens approached complete opacification, however, the refraction changed toward emmetropia or even myopia. Helminen [44] described early loss of accommodation, which he considered to be a precursor of beginning cataract.

In a minority of instances the lens opacities became arrested and vision was retained. Lindberg [45] described 2 patients who showed water slits beneath the anterior capsule, no golden reflex and a series of white, isolated granules lying in front of the supranuclear layers both in front of and behind the lens. Three years after the administration of dinitrophenol was stopped the corrected vision remained at 6/5. One patient of mine with stationary lenticular changes and vision 1.0 (?) had a greatly weakened accommodation (a + 2.25 D. sph. addition at the age of 46). Whedon [41o] recorded specklike opacities and a golden reflex in 1 patient. Five months later scarcely any trace of the opacities could be found in the lenses or the capsules. Bedell [52] and Hessing [41s] added 4 cases in which the condition did not progress.

The interval which elapsed between the onset of blurred vision and complete opacification of the lens varied between seven days and five months, with an average of two and one-half months. The early changes progressed much more slowly than the later ones, as is illustrated by the earliest case I observed (case 3 [38]). The patient presented characteristic lenticular changes but retained a vision of 0.8 + for more than two and one-half months, only to become blind (vision reduced to perception of hand movements) within the next eight days!

Onset.—Cataracts appeared after an average of fifteen months' treatment in 27 patients (Rodin [41d]). In 67 per cent of these, treatment had been stopped before lenticular changes occurred. The interval between

52. Bedell, A. J., in discussion on Horner.[41m]

the termination of the administration of the drug and the appearance of symptoms of cataract varied from a month to a year, with an average of seven months.

Dose.—The length of time that dinitrophenol was taken and the amount of the drug consumed varied widely. Rodin [41d] found that in 29 cases the duration of treatment varied from three months to twenty-four months, with an average of eleven months. The amount of drug taken as estimated by Rank and Waldeck [41l] varied from a minimum of 9 Gm. to a maximum of 126 Gm., the average being 73 Gm. Neither the length of treatment nor the total dose seemed to have any bearing on the occurrence of cataracts. Individual susceptibility appeared to be a more important factor.

Age and Sex.—Only 3 males are believed to have acquired cataracts from the use of dinitrophenol. Cogan and Cogan [19d] and Rundles [41a] reported 1 case each, whereas the third came to my attention in San Francisco.

The average age in 32 cases was 45 years. The youngest patient was 30 and the oldest 67 (Rodin [41d]). Seventy per cent were in the third or fourth decade. Two patients aged 25 years have been reported on. Hessing [41s] mentioned a mother and her daughter who were operated on for cataract at about the same time.

Incidence.—In a paper published in 1937 I [41m] estimated that the incidence of cataracts in patients who had taken dinitrophenol was probably between 0.1 and 1 per cent and that the total number of patients affected would range between 60 and 100.

There are only a few reports of extensive clinical studies of dinitrobodies to be found in the literature. The data available show that Tainter, Stockton and Cutting [8n] (1935) reported 1 case among 170 treated patients; Hill [41c] (1936), 1 among 68; Simkins [15g] (1937), 1 among 159; Måhlén [51] (1938), 1 among 66 of Berglund's 73 patients who received dinitroorthocresol. The incidence averages 0.86 per cent, which is within the estimate previously given. Since the interval between the discontinuance of the drug and the occurrence of cataract may be as long as one year, some of the patients treated in these four series may have acquired cataracts at a later time. This figure is, therefore, more likely to be minimum than maximum. My previous estimate of the number of persons affected proved much too low. I have recently collected a total of 177 cases from the literature up to January 1941. Of these, the cataracts in 164 followed the use of dinitrophenol, whereas in 13 dinitroorthocresol had been taken. These figures also are probably too low. It is certain that additional cases have occurred which have not been reported in the medical journals. Some cases may have been presented before local medical societies. Since proceedings of relatively

few of these societies are published, such cases are lost sight of. In isolated cases cataracts have resulted from the use of patent slimming nostrums. Five of these were reported as late as 1938,[41w] but such cases are now most likely to be mentioned in *The Journal of the American Medical Association* in the section devoted to the investigation of patent medicine frauds.[53]

Treatment.—Medical treatment failed to cause regression or to prevent the progress of any of the cataracts reported. Although a few "arrested cases" have been reported, which are discussed under the heading "Lenticular Changes," with one exception the arrest was not attributed to the treatment. Local measures, such as application of hot compresses, use of ethylmorphine hydrochloride and subconjunctival injections, proved useless. General therapy, consisting of forcing fluids and administering calcium salts, cevitamic acid (vitamin C) and lens antigen, was equally ineffective.

Surgical Considerations.—Operative treatment was successful in a high percentage of patients. The technic was not difficult, and the results were in general probably better than the average for an equal number of senile cataract extractions, because of the fact that the eyes were in healthier, younger bodies.

While the technic varied with the preference of the operator and the age of the patient, the majority of the cataractous lenses were removed by one of the procedures applicable to the extraction of soft cataract, with preservation of a round pupil.

As a reasonable cross section of surgical experience with cataract due to dinitrophenol, I have analyzed the combined operative reports of three surgeons who have published their findings in a substantial series of cases, namely Hessing[41s] (25 cases), H. Barkan and others[41g] (20 cases) and myself[41m] (17 cases). Of a total of 62 cataract extractions, a Graefe incision was made in 42 (67.7 per cent), while a keratome was used in 20 (32.2 per cent). There was a peripheral iridectomy in 30 cases (48.4 per cent), no iridectomy in 18 (29 per cent) and a full iridectomy in 14 (22.6 per cent). Extracapsular extraction was done in all cases (100 per cent). The complications that occurred consisted of prolapse of the iris, 1 case; secondary glaucoma, 2 cases; iritis, 3 cases; loss of vitreous, 3 cases; postoperative bleeding, 4 cases, and secondary cataract, 12 cases. Further comment concerning secondary cataract will be made later on. Vision of 15/20 or better was obtained in 86 per cent of the series, and the average visual result for the 62 patients was 17/20 + at the preliminary or the final refraction.

53. Dilex-Redusols: A Dinitrophenol Nostrum Declared Fraudulent and Debarred from the United States Mails, Report of the Bureau of Investigation, J. A. M. A. **106**:1587 (May 2) 1936.

The surgical treatment of cataract due to dinitrophenol thus presented no particular difficulties. Certain peculiarities, however, are worthy of mention. The lens was usually soft, sometimes lardaceous and less often firm, as in senile cataract. The lens was delivered in fragments, rather than en masse. Lens debris present postoperatively was unusual, since most of the fibers were opaque and could be removed completely at the time of operation. Intracapsular extraction was seldom employed, since, because of the taut, swollen nature of the lens, it could apparently be performed only with difficulty and was regarded as unnecessary. Acute secondary glaucoma was treated in a minority of cases by the Graefe or some other basal type of iridectomy. The majority of operators proceeded as in a soft cataract extraction, disregarding the swollen lens by a bold incision. The results were equally good in relieving tension and better as regards the cosmetic result.

In the great majority of cases secondary cataract developed eventually, as may be demonstrated by a late analysis of my own series of cases. I have not seen any comment in the literature concerning this point. In 17 of 19 cases in which I have follow-up records, 15 discissions were either performed or advised, a startling incidence of 88 per cent. Many of these operations were necessary two years or more after the original extraction. This figure is the more remarkable when it is compared with an incidence of only 5 needlings after 32 extracapsular extractions of senile cataract (15.62 per cent) which I performed during the same period. The explanation for this phenomenon lies, I believe, in the preponderant number of young lenses encountered in the extractions of cataracts due to dinitrophenol. The formation of secondary cataract is in keeping with the proliferative activity of the capsule, which suggested to older writers the expression "regeneration of the lens" (Milliot; Textor,[54] 1872). Duke-Elder [55] stated that this phenomenon "occurs preferentially but by no means exclusively in younger patients and concerns especially the subcapsular epithelium." Youth is, therefore, more of a factor than inflammatory reaction, (1) since the secondary cataract occurred long after the operation and (2) because the average reaction was no greater and in most cases was less than after extracapsular extraction of senile cataract.

ETIOLOGY

The etiology of cataract following the use of dinitrophenol is not understood. There is even a lack of agreement in the classification of the form of lens. Although some American authors speak of dinitrophenol cataract as a new type, others in Europe and in America, mindful of the

54. Textor, K., quoted by Duke-Elder.[55]

55. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 3236.

early changes in the posterior part of the lens, use the term "complicated cataract," a conception introduced by Becker in 1876 but later amplified, particularly by the slit lamp studies of Vogt in 1919. Duke-Elder [56] considered dinitrophenol cataract under the head of "toxic cataract." European writers often combine dinitrophenol and dinitroorthocresol under the collective term "dinitro bodies" and designate the lens opacities as dinitro cataract. Moreover, the relationship of cataract to the ingestion of dinitro bodies remains unconfirmed.

In favor of such an etiologic relationship one may point out that after treatment with these drugs cataracts occurred in many women who were too young to have senile cataracts and too healthy to have lenticular changes due to other causes. It may be admitted further that dinitro bodies are toxic substances capable of causing death or severe poisoning in man and in animals; that susceptibility to these substances varies remarkably, and that in carefully controlled doses, without side reactions, there is an unnatural stimulation of metabolism and an increase in oxidative processes within the body. Is it not possible that toxic effects or the increased oxidation may affect the delicate metabolism of the lens, a subject about which so little is known? These statements, while true, and the question, while reasonable, are unanswerable in the present state of knowledge.

In speaking against such an etiologic relation one may say that similar cataracts have been reported in healthy young women who had not taken dinitrophenol (Horner [41m]; Barkan and Bettman [57]) and that similar cataracts have been seen by ophthalmologists in association with such conditions as diabetes and goiter, as was emphasized by Bedell.[52] If there is a toxic basis, why should lenticular changes appear only once in about 116 patients, and why should they occur as late as a year after the drug has been eliminated from the system? Why did not cataract develop in munitions workers who were constantly exposed to dinitrophenol during the first World War? Why have not lenticular changes developed in experimental animals given dinitrophenol? Here, too, are statements which are true and reasonable questions that must for the present remain unanswered.

Although many of the contributors to the literature of dinitro cataract have offered suggestions as to the mechanism involved, the majority of these are merely speculative and are not supported by experimental evidence. There are relatively few reports in the literature of investigations covering this phase of the problem. These will be reviewed, together with the suggested explanations of various authors previously mentioned.

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56. Duke-Elder,[55] p. 3154.

57. Barkan, H., and Bettman, J. W.: Am. J. Ophth. **21**:165, 1938.

Knowledge of the etiology of cataract in general is gradually increasing, but even in the case of types which can be produced experimentally, such as the cataract which follows the use of betanaphthol or thallium, it is still impossible to say why these changes take place.

Animal Experiments.—Tainter and his co-workers [58] have been unable to produce pathologic ocular changes in any of the common laboratory animals by dinitrophenol administered under a variety of conditions. White rats, for example, which are generally susceptible to formation of cataract, have been fed diets containing up to fatal concentrations of dinitrophenol from the time they were weaned until death occurred about two years later, without showing any pathologic changes in the eyes.

Other feeding experiments have been carried out by Helminen [44] and Basile [59] with rabbits, by Sohr [60] with guinea pigs, by Nordmann and Reiss [61] with rabbits and rats and by Ciotola [49] with rats, rabbits and dogs. All these workers achieved equally negative results. Ciotola injected dinitrophenol directly into the anterior chamber and the vitreous of animals without producing cataracts.

Krause,[62] in commenting on the toxic substances that may injure the lens directly or indirectly, pointed out that in rats thallium poisoning results in the formation of cataract, whereas in man the optic fibers are destroyed. This observer stated the belief that this fact indicates a difference in the metabolism of species and may explain the failure to induce cataracts in rats by giving them dinitrophenol.

Dinitrophenol and Lens Metabolism.—The effect of dinitrophenol on the lens metabolism was studied by Field, Tainter, Martin and Belding.[63] These workers postulated that if the lens was unusually responsive to dinitrophenol, the ordinary therapeutic dose might stimulate its respiration to such a degree that products of metabolism would accumulate faster than they could be carried off and nutritional opacities would result. Their results proved this assumption to be false. The oxygen consumption of the lens was low in the mean, as compared with that of striated muscle and rabbit retina, whereas with optimum concentrations it was also lower than that of muscle and about equal to that of the retina. Whether the lens would deteriorate from this heightened respiratory rate was not determined, but that it would was regarded as possible.

58. Tainter, M. L.: J. Pharmacol. & Exper. Therap. **63**:51, 1938.
59. Basile, G.: Ann. di ottal. e clin. ocul. **67**:223, 1939.
60. Sohr, H.: Arch. f. Ophth. **138**:332, 1938.
61. Nordmann, J., and Reiss, P.: Compt. rend. Soc. de biol. **123**:233, 1936.
62. Krause, A. C.: Am. J. Ophth. **21**:1343, 1938.
63. Field, J., II; Tainter, E. G.; Martin, A. W., and Belding, H. S.: Am. J. Ophth. **20**:779, 1937.

Permeability of the Capsule.—Studies were made by Borley and Tainter [64] to determine the effect of dinitrophenol on the permeability of the lens capsule. This question had been brought up by Vogt [46b] and others in connection with glaucoma, which sometimes occurred in association with dinitro cataracts. Two possibilities had been suggested by Krause [65] for other types of cataract in 1934, namely a decrease in the permeability of the capsule, which might prevent normal exchange of metabolites, and an increase which might allow foreign materials to penetrate into the lens or essential elements in the lens to escape. Borley and Tainter found no basis for assuming that dinitrophenol alters the permeability of the capsule either in vitro or in vivo.

Vitamin Deficiency and Dinitrophenol.—Tainter and Borley [66] could not produce cataract in animals suffering from deficiencies of vitamin A, B_2 or C by feeding them dinitrophenol in maximum tolerated doses. They made their investigation in order to determine whether possible vitamin deficiencies in patients undergoing weight reduction with dinitrophenol might predispose the lens to the formation of cataract.

Lactose Cataracts and Dinitrophenol.—Borley and Tainter [67] included dinitrophenol in various cataract-producing lactose diets in white rats in order to determine whether the addition of the drug affected the lenticular changes in any way. They found that the added dinitrophenol did not alter the average time of appearance, the progression or the magnitude of the lens opacities. They also demonstrated that using dinitrophenol from three different manufacturers produced no variation in their results. Ciotola [49] in 1937 had also certified as to the purity of the dinitrophenol with which he had obtained negative results in animal experiments. He later observed the development of cataract in a patient who had taken the drug from the same source. The contention of Dally [68] that impurities in dinitrophenol, especially dinitronaphthol, are the cause of cataract has been disproved repeatedly. Other experimenters [67] demonstrated that dinitrochlorobenzene, a possible impurity of commercial dinitrophenol, would not produce cataract in animals. In the reports of the original munitions experiments (Mayer [69]) the French stated that certain common impur-

64. Borley, W. E., and Tainter, M. L.: Effects of Dinitrophenol on Permeability of Capsule of Lens, Arch. Ophth. **18**:908 (Dec.) 1937.

65. Krause, A. C.: The Biochemistry of the Eye, Baltimore, Johns Hopkins Press, 1934.

66. Tainter, M. L., and Borley, W. E.: Influence of Vitamins and Dinitrophenol on Production of Experimental Cataract, Arch. Ophth. **20**:30 (July) 1938.

67. Borley, W. E., and Tainter, M. L.: Am. J. Ophth. **21**:1091, 1938.

68. Dally, P.: Concours méd. **50**:3491, 1935; Arch. Soc. d. sc. méd. et biol. de Montpellier **17**:109, 1936.

69. Mayer, A., quoted by Perkins.[5]

ities, such as mononitrochlorobenzene and chloronitrophenol, are less toxic than the dinitrophenol itself.

Oxidation-Reduction Potential.—Nordmann and Reiss [61] investigated the effect of dinitrophenol on the oxidation-reduction potential of the aqueous and the lens in rabbits. After four injections of the drug, the potential of the aqueous was increased by 17 per cent and that of the lens by 37 per cent. The rise persisted after cessation of the treatment.

Other Suggestions.—Krause [62] expressed the belief that dinitro cataracts may be caused in part by interference with the creatine and adenosine-phosphate processes in the lens.

H. Barkan, Borley, Fine and Bettman,[41g] in discussing the etiology of dinitro cataracts, referred to the role of vitamin C in normal and in cataractous lenses. While cevitamic acid was used by Josephson [40b] in the treatment of an early dinitrophenol cataract, a specific relation to vitamin C is unproved. Barkan and others suggested the possibility of a disturbance of the nutrition of the lens or a p_H altered toward the acid side as a potential factor. No estimation of the p_H of the lens in dinitrophenol cataracts has, to my knowledge, appeared in the literature. In the case of naphthalene cataracts, Reiss and Nordmann [70] have found that only lenses removed during the initial stages of opacity showed the expected increase in acid content. Mature cataracts revealed a shift toward alkalinity, the average being 7.8, from the range (p_H 7.1 to 7.5) for normal rabbit lenses.

I have seen no previous comment as to the possible role of lactic acid in the production of the changes in the lens. Dinitrophenol, by increasing oxidation, raises the lactic acid content of the blood. Since it is known that the lactic acid content of the aqueous always exceeds that of the blood, it is conceivable that during treatment it might rise to such heights as to be harmful to the lens epithelium. Changes in the lens during treatment might continue to progress after the drug was discontinued. No estimation of the lactic acid content of the aqueous during the administration of dinitrophenol has apparently been published. Biozzi [71] has produced cataracts in animals by inducing experimental asphyxia, explaining them by the uncompensated acidosis that prevails during asphyxia.

Müller [72] attributed changes in the lens to the increased oxidation by dinitrophenol.

Jackson [73] stated that it is conceivable that this drug breaks through the protective function of the lens capsule, which is to preserve trans-

70. Reiss, P., and Nordmann, J.: Compt. rend. Soc. de biol. **128**:111, 1938.

71. Biozzi, C.: Arch. f. Ophth. **133**:423, 1935.

72. Müller, H. C.: Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **51**:370, 1936.

73. Jackson, E.: Am. J. Ophth. **19**:431, 1936.

parency. Toxic effects on the subcapsular epithelium would disturb its important functions of growth and nutrition and might explain the special distribution of the opacities and their characteristic late appearance.

Cogan and Cogan [40d] also suggested damage to the lens epithelium as an etiologic factor but stated the belief that this is the result of tissue anoxema.

Onfray and Gilbert-Dreyfus [24d] stated the opinion that a cataract may be an expression of hepatic damage caused by dinitrophenol and a disturbance of water metabolism. They connected the latter with the frequency of associated glaucoma.

Résumé.—I conclude my remarks on the etiology of the formation of cataract following the use of dinitrophenol with the same statements with which I started, i. e., that the etiology is not known and that the cause and affect relation is undefined. An impasse has been reached in this problem, since the drug is no longer being administered to human beings and all attempts to produce cataracts by giving it to animals have been unsuccessful.

SUMMARY

1. The pharmacologic properties of four phases in the use of dinitrophenol are traced: (*a*) as a laboratory curiosity in 1895, (*b*) as a health hazard in the munitions industry (1914 to 1918), (*c*) as a metabolic stimulant with possible clinical applications (1933) and (*d*) as a potent drug which was used in the treatment of obesity (1934-1935) and which exhibited certain unfortunate side reactions.

2. The majority of these reactions were trivial, a few were fatal and a middle group, affecting the skin and the blood, were severe, but the most serious of all was the development of cataracts.

3. Cataracts occurred with recommended doses of the drug and without other demonstrable reactions.

4. Cataracts developed in a total of more than 177 persons after the use of either dinitrophenol or dinitroorthocresol, an estimated incidence of 0.86 per cent. Of the patients, 98 per cent were women who averaged about 45 years of age.

5. The cataracts were all of one type, were bilateral, developed rapidly, were accompanied with visual loss and occurred at any time up to a year after the drug had been discontinued.

6. Medical treatment was without effect, but surgical extraction proved successful, excellent visual acuity being obtained in a large percentage of cases.

7. Late secondary cataract was of frequent occurrence after extraction, as was shown by a reported incidence of 88 per cent in one series.

8. All attempts to produce experimental cataracts in laboratory animals by various and repeated doses of dinitrophenol have been successful.

9. Dinitrophenol does not alter the permeability of the lens in vivo or in vitro, nor does it increase inordinately the oxygen consumption of the lens as compared with other tissues. It does not hasten or otherwise affect the artificial production of lactose cataracts in animals.

10. The cause of cataracts following the treatment of obesity with dinitro bodies is unknown, and its relation to the ingestion of these substances is unproved. The argumentative strength of post hoc, ergo propter hoc, cannot be denied, however. This argument has been used successfully to obtain monetary damages in medicolegal actions filed by patients.

11. Since the dinitro compounds found widespread and generally enthusiastic acceptance because of the beneficial results they produced, it is regrettable that they had to be discarded because of the secondary reactions. Additional studies are therefore needed to determine whether related products may not be developed that will retain the metabolic potency with a lessened amount of untoward effects or even their complete absence. Some attempts along this line have proved at least partially successful,[74] and others will doubtless be made. The chief deterrent to such studies is the necessity of being certain that the animal experiments can safely be used as guides to the potential clinical toxicity of the compounds elaborated.

CONCLUSIONS

1. Dinitrophenol has been demonstrated to be a potent metabolic stimulant and an efficient oxidizer of excess body fat.

2. Its physiologic actions are highly desirable and can be utilized in the treatment of a number of abnormal body states.

3. The occurrence of toxic reactions, particularly the formation of cataract, contraindicates further therapeutic use of this drug until these are understood and can safely be eliminated.

4. Should their elimination prove infeasible, some other less toxic substitute may be developed through the knowledge that has accumulated in the study of dinitrophenol.

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74. Wesson, L. G.: J. Am. Chem. Soc. **62**:3466, 1940.

A MODEL OF THE VISUAL PATHWAYS

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It is the purpose of this communication to describe a model of the visual pathways which was constructed in conjunction with Dr. David G. Cogan and used in the graduate course in ophthalmology at the Harvard Medical School. While brain modeling is a well established procedure in neurologic teaching, it appears to have been used relatively little in ophthalmologic courses. Mayer [1] recently described a model for demonstration purposes, but the model here described has the advantage over Mayer's in that it may be easily constructed by each student. By making a model himself a student can best acquire a three dimensional idea of the visual pathways and of their anatomic relationships.

Gross and microscopic brain sections are available, and each student is encouraged to obtain his information independently from these specimens and from various textbooks of neuroanatomy.

INSTRUCTIONS GIVEN TO STUDENT

Materials Needed.—The following materials are used for each model:

Plywood, 1 foot (33 cm.) square
Baseboard, 1 foot square
Plasticene, several colors
Brass rod, 8 inches (20 cm.)
Brass wire, 8 to 10 feet (244 to 304 cm.)
Brass track, 1 foot
Stiff celluloid strip, 2 by 6 inches (5 by 15 cm.)
White twine
Fine wire
Tools, bit and brace, etc.

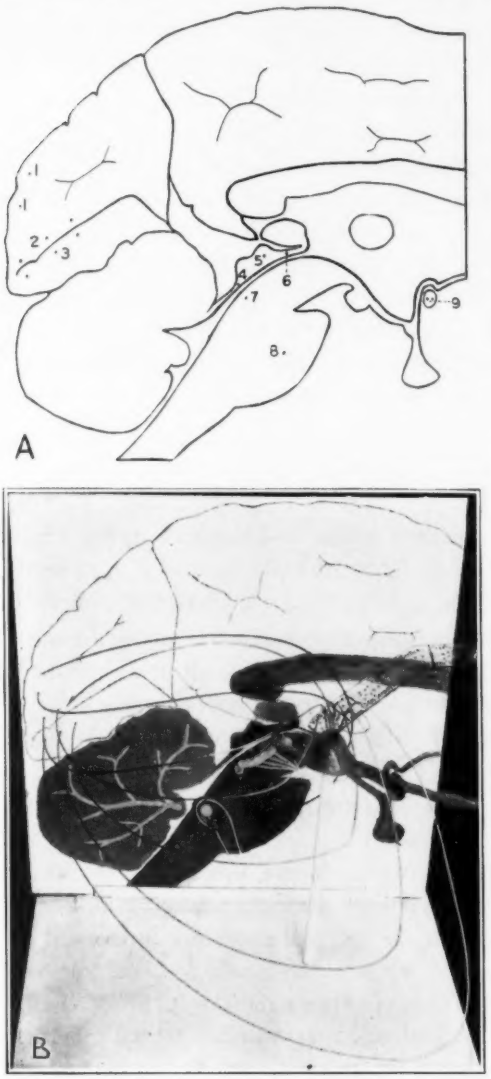
Procedure.—1. A photograph of the mesial surface of a parasagittal section of the brain (such as that shown by Whitnall [2]) is projected and traced on the plywood.

2. Holes are drilled in the plywood as numbered in *A* of the accompanying illustration.

From the Howe Laboratory of Ophthalmology.

1. Mayer, L. L.: The Optic Pathway, Arch. Ophth. **23**:382 (Feb.) 1940.

2. Whitnall, S. E.: The Anatomy of the Human Orbit, London, Oxford University Press, 1932, p. 407.



A, outline of a parasagittal section of the brain (modified from Whitnall [2]). The holes may be identified as follows: *1*, for corticofugal fibers running from the peristriate area to the superior colliculus and the pons; *2*, for optic radiations entering the upper lip of the calcarine fissure; *3*, for optic radiations entering the lower lip of the calcarine fissure; *4* and *7*, for fine wire emerging from hole *7* (at the fourth nerve nucleus) and arching around the aqueduct to pass through hole *4* (when brought back through hole *4* this wire represents the decussated fourth nerve from the opposite side of the brain stem); *5* and *8*, for the corticofugal fibers leaving hole *1*, and *9*, for a continuous brass wire passing through anterior hole *9* and back out through posterior hole *9* (it then arches laterally, running through the hole in the top of the brass tube, ending at hole *6*, in the pretectum—see the seventh step in the procedure). *B*, the completed model.

3. The brain stem, colliculi, pineal body, corpus callosum, pituitary body and cerebellum are modeled onto the plywood with plasticene, as shown in *B* of the accompanying illustration.

4. The important motor and sensory nuclei of the brain stem are placed in their appropriate positions as shown by Ranson.[3] The third nerve nucleus is arched dorsolaterally by molding the plasticene around a short, bent brass wire (figure, *B*). The Edinger-Westphal nucleus is represented between the anterior horns of the third nerve nucleus. Short lengths of white twine are used to indicate the fibers forming the third nerve. The modeling of the fourth nerve is described in the legend to the figure, *B*. A curved brass wire embedded in the plasticene represents the sixth nerve coursing above and around the nucleus of the seventh nerve.

5. The plywood is fastened to the baseboard by means of a brass track (figure, *B*).

6. A hole is drilled in the baseboard 3 inches (7.6 cm.) from the plywood and 1 inch (2.5 cm.) anterior to the pretectal region. The brass tube inserted in this hole supports the lateral geniculate body.

7. A continuous brass wire is used to carry the optic nerve, chiasm and optic tract. It passes through a small hole drilled through the brass tube ¼ inch (0.6 cm.) from the top and, coursing toward the pretectum, forms the brachium of the superior colliculus. It thus represents the continuation of the pupillomotor pathways.

8. The optic radiations are represented by curved brass wires running from the top of the brass tube (lateral geniculate body) to the area representing the occipital cortex. These wires, all of which emerge from the dorsal aspect of the lateral geniculate body, course vertically through the posterior limb of the internal capsule, represented by the angulated celluloid strip. The wires corresponding to the superior retinal quadrants pass directly posteriorly to the dorsal lip of the calcarine fissure, while those corresponding to the inferior retinal quadrants pass ventrolaterally, wind around the anterior horn of the lateral ventricle (forming "Meyer's loop") and end in the ventral lip of the calcarine fissure (figure, *B*).[4]

9. Two wires are run from the peristriate areas through the internal capsule. One goes to the superior colliculus and the other, passing

3. Ranson, S. W.: The Anatomy of the Nervous System, ed. 5, Philadelphia, W. B. Saunders Company, 1936, p. 166.

4. Behr, C.: Die Erkrankungen der Sehbahn vom Chiasma aufwarts, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1931, vol. 6, p. 254. Ranson,[3] p. 218.

anteriorly to the lateral geniculate body, ends in the pons. These are corticofugal pathways concerned with conjugate vertical and lateral deviation of the eyes.

10. The continuous brass wire representing the optic nerve, optic tract, chiasm and brachium of the superior colliculus is covered with plasticene. The lateral geniculate body, shaped like a Napoleonic cocked hat, is modeled at the top of the brass tube.

11. The celluloid strip representing the internal capsule can be marked off in india ink to show the anatomic relationship between the visual and other motor and sensory pathways.[5]

12. Finally, the model is sprayed with two coats of shellac.

243 Charles Street.

5. Morris, H.: Human Anatomy, ed. 8, Philadelphia, P. Blakiston's Son & Co., 1925, p. 924.

SODIUM, CHLORIDE AND PHOSPHORUS MOVEMENT AND THE EYE

DETERMINED BY RADIOACTIVE ISOTOPES

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W. MORTON GRANT, M.D.

DAVID G. COGAN, M.D.

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BOSTON

The rate of accumulation of sodium, chloride and phosphorus in the normal anterior chamber of the rabbit was determined after isotopes of these elements possessing artificially induced radioactivity were introduced into the blood. This research is an extension of the recent study made by some of us [1] in which it was shown that water in the anterior chamber exchanges with that in the blood stream at a rate greatly in excess of the so-called rate of formation of whole aqueous.

A comparison of the rate of water movement (50 cu. mm. per minute) with that given for formation of the whole aqueous [2] (1 to 2 cu. mm. per minute) would suggest that some other constituents, such as sodium or chloride, enter the anterior chamber at a rate considerably less than would be indicated by their final concentrations in the aqueous (about one unit of sodium chloride per hundred of water). In other words, it may be that water is moving independently of these constituents. The experimental findings to be presented in this paper support this idea and indicate that the so-called rate of formation of aqueous is more directly related to the movement of substances other than water, e. g. electrolytes.

TECHNIC

The artificially radioactive elements used in this study were separately prepared in the cyclotron at Harvard University in the following manner:

Elemental sodium (Na^{23}) was bombarded by deuterons to form radioactive sodium (Na^{24} [half-life 14.8 hours]). The radioactive sodium was then dissolved in

From Howe Laboratory of Ophthalmology, Harvard Medical School, and Jefferson Physical Laboratory, Harvard University.

1. Kinsey, V. E.; Grant, M., and Cogan, D. G.: Water Movement and the Eye, Arch. Ophth. **27**:242-252 (Feb.) 1942.

2. Friedenwald, J. S., and Pierce, H. F.: Circulation of Aqueous: I. Rate of Flow, Arch. Ophth. **7**:538-557 (April) 1932.

absolute ethyl alcohol and titrated to neutrality with concentrated hydrochloric acid. The ethyl alcohol was removed and the sodium chloride containing radioactive sodium (Na^*Cl [asterisks indicate atoms possessing radioactivity]) formed was made isotonic with the blood.

To prepare radioactive chlorine (Cl^{38}), lithium chloride was bombarded with deuterons. Because the decay of radioactive lithium is so rapid (half-life 0.88 second) no appreciable error is introduced by the lithium when the radioactive chloride is injected in the form of lithium chloride ($LiCl^*$). Nevertheless, decay curves were made for the recovered radioactive chloride, and it was found to contain an insignificant contribution from the remaining lithium.

To obtain radioactive phosphorus (P^{32}), a mixture of iron phosphides was bombarded with deuterons, the contaminating impurities were removed and from the radioactive phosphorus (half-life 14.3 days) disodium hydrogen phosphate ($Na_2HP^*O_4$) was prepared [3] by the method of Chapin and Ross.[4] This was used for injection.

In the experiments designed to measure the rate of accumulation of radioactive isotopes in the anterior chamber the injections were made intraperitoneally into rabbits, about 5 cc. of solution being used in each instance. Plasma was obtained by withdrawing blood by cardiac puncture into a small amount of dry heparin and throwing down the cells by centrifugation. After the topical application of an anesthetic (2 per cent pontocaine), aqueous was withdrawn for the eyes into especially constructed microsyringes. The syringes were accurately calibrated so that the volume of the aqueous could be determined to $\pm$ 0.002 cc., or to about $\pm$ 1 per cent.

In the experiments designed to measure the rate of disappearance of radioactive sodium from the anterior chamber, the aqueous was first withdrawn, and immediately the same quantity of isotonic sodium chloride (Na^*Cl) solution was injected. The needle (no. 27) was cut off and sealed as previously described.[1] After varying intervals a second puncture was made, and the amount of radioactivity remaining in the fluid in the anterior chamber was determined in the usual manner.

An electroscope was used to determine the radioactivity of the samples, the beta and the gamma rays being measured together. In the first few experiments with sodium, and in all the work with chloride, about 0.3 cc. of plasma and the measured samples of aqueous were placed separately on pasteboard cards, the edges of which were coated with paraffin to form a well. The cards were then allowed to dry, and a single layer of cellophane tape was pasted across the dried sample. In a few of the early experiments with sodium chloride (Na^*Cl) it appeared that a different amount of self absorption of the emitted beta rays occurred for the aqueous and for the serum, owing, presumably, to their differential penetration into the pasteboard. A correction was therefore applied, and the technic was modified slightly for the phosphorus experiments by the pasting of sheet aluminum on the cards. A further modification, which was used in 8 of the 10 sodium experiments and which appears to be highly satisfactory for this kind of work, consisted in placing the samples in the depression of hanging drop glass microscope slides. After evaporation to dryness the sample was protected with a piece of cellophane tape.

All the radioactivities measured have been mathematically adjusted to allow for the different proportions of solid matter present and are expressed on a kilo-

3. Dr. J. F. Ross performed these operations for us.

4. Chapin, M. A., and Ross, J. F.: To be published.

gram of water basis. In order to simplify the presentation of the results the maximum amount of radioactivity found in the plasma of each animal has been arbitrarily assigned a value of 100 per cent. All other values have been adjusted to the same scale.

RESULTS

Chart 1 shows the results of giving 10 rabbits intraperitoneal injections of radioactive sodium in the form of physiologic solution of sodium chloride (Na*Cl). The level of the radioactive sodium in the plasma remained remarkably constant after reaching a maximum. Except in 1 animal (indicated at 155 and at 167 minutes on the curve for aqueous)[5] the radioactive sodium may be seen to have accumulated in the anterior chamber in regularly increasing amounts with time, reaching 50 per cent of the plasma level after approximately fifty-five minutes. It may be seen from the curve for aqueous that approximately forty minutes would

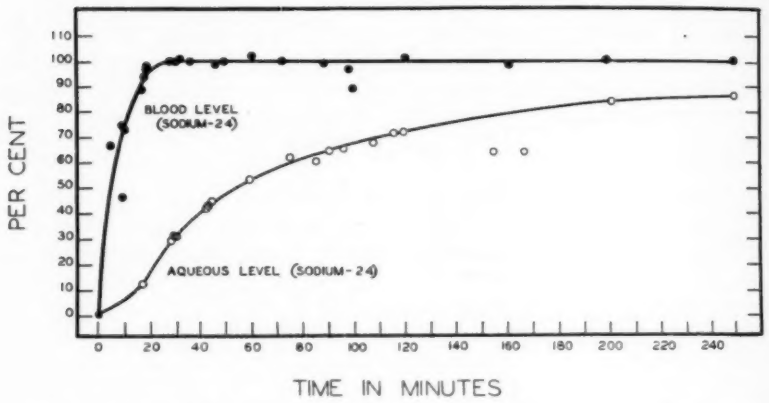

Chart 1.—Distribution of radioactive sodium (Na^{24}) between the blood and the aqueous humor after intraperitoneal injection.

have been required had the level in the blood been constant from the beginning.

The results of determining the amount of radioactive sodium remaining in the anterior chamber of 7 eyes after replacement of aqueous with isotonic solution of sodium chloride containing radioactive sodium were

5. The volume of the anterior chamber in this animal was 350 cu. mm., as compared with an average volume for 17 other anterior chambers of 258 cu. mm. These results, together with several previous observations on water exchange, indicate that the rate of accumulation of the test substances is appreciably less in large anterior chambers than in anterior chambers of average size. What appears to be an abnormally low concentration of radioactive chloride (chart 2, curve for aqueous, the point at 30 and at 57 minutes) was also found in a rabbit possessing an abnormally large anterior chamber (348 cu. mm.).

not as consistent as those shown for the former procedure (chart 1). They do indicate, however, that only about 50 per cent remains in the anterior chamber after eleven minutes and only about 20 per cent after twenty-two minutes. This fact would strongly support evidence from a variety of other sources that any preliminary manipulation involving the anterior chamber prior to testing of the permeability properties of the blood-aqueous barrier in itself increases the permeability to these test substances.

Several purely exploratory experiments in which radioactive sodium was traced from the blood to the cornea, the lens and the vitreous indi-

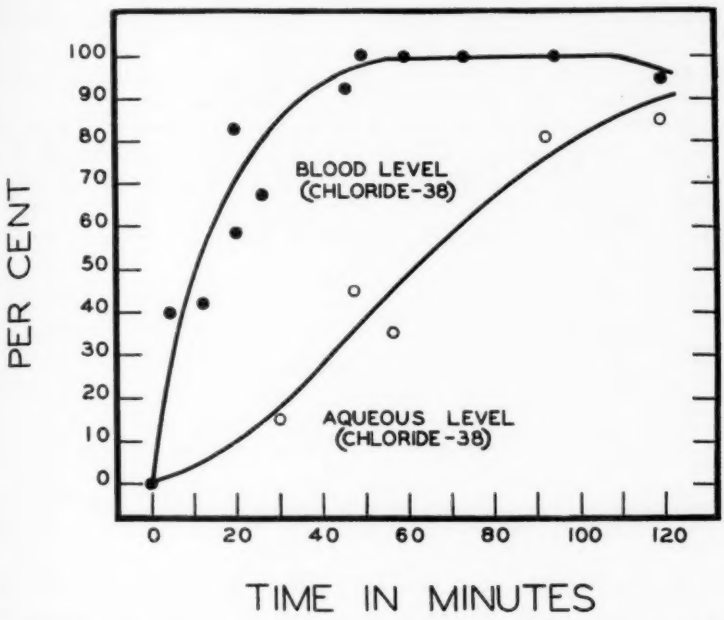

Chart 2.—Distribution of radioactive chloride (Cl^{38}) between the blood and the aqueous humor after intraperitoneal injection.

cated that the level reached within the first hour in the cornea was of the same order of magnitude as that in the aqueous, while that in the lens and that in the vitreous were much lower.

The relative concentration of radioactive chloride in the aqueous as compared with that in the plasma after injection of lithium chloride solution containing radioactive chloride (LiCl*) intraperitoneally into rabbits is shown in chart 2. The rate of accumulation of chloride in the anterior chamber appears to be approximately the same as that for sodium. Unfortunately, the points on the curve for aqueous at 30 and at 57 minutes represent an anterior chamber of above average size (348 cu. mm.).[5]

Because the level of radioactive phosphorus in the blood was so variable the results of the experiments with this substance were not graphed but were recorded separately in table 1. Here the relative concentrations of radioactive phosphorus in plasma and in aqueous are shown. The top half of the table refers to the concentration in aqueous and in trichloroacetic acid filtrates of plasma, while the lower portion of the table gives the concentrations in aqueous and in whole plasma in different animals. Presumably the former indicates inorganic phosphorus, largely in the form of phosphate, while the latter represents total phosphorus. It is not readily possible to compare quantitatively the rate of accumulation of radioactive phosphorus in the anterior chamber with that for sodium and chloride. It can be seen, however, that the rate for

Distribution of Radioactive Phosphorus Between the Blood and the Aqueous Humor After Intraperitoneal Injection (5 Animals)

Time After Injection, Minutes	Concentration of P^{32}, Units of Activity per Kg. of Water		Time After Injection, Minutes	Concentration of P^{32}, Units of Activity per Kg. of Water	
	Plasma Filtrate *	Aqueous		Plasma Filtrate *	Aqueous
10†	57	..	8	92	..
17	80	..	16	100	..
25	100	8.0 (4 eyes)	25	95	8.7 (2 eyes)
	Whole Plasma	Aqueous		Whole Plasma	Aqueous
25	100	..	27	100	..
54	76	..	51	60	..
77	61	..	62	..	12
78	..	13.4	63	..	13
80	..	15.4	75	43	..
100	41	..	100	28	..
200	16	..	200	11	..
400	14	..	400	7	..

* Inorganic radioactive phosphorus determined in trichloroacetic acid filtrate.
† Two animals—duplicate values for plasma and for the phosphorus level in the aqueous.

phosphorus is much lower than that for sodium and chloride. Whether the differences are due to size or to charge of radical will be discussed in a subsequent communication.

COMMENT

It is interesting to note that the reported rate of formation of aqueous, i. e. 1 to 2 cu. mm. per minute,[2] is of the same order of magnitude as that found for the accumulation of sodium and chloride. Sodium and chloride appear to enter the anterior chamber at a rate calculated to be approximately equivalent to 4 cu. mm. per minute of whole aqueous. This, as was pointed out in the introduction, is in contrast to the 50 cu. mm. per minute reported previously [1] for water. It would now appear that measurements of the formation of whole aqueous involving volume changes indirectly indicate the electrolyte net volume changes and show that water movement is only coincidental.

SUMMARY

The rate of accumulation of sodium, chloride and phosphorus in the anterior chamber of the rabbit has been measured through the use of the radioactive isotopes of these elements. It was found that sodium and chloride enter the anterior chamber from the blood stream at rates sufficient to produce 50 per cent of the concentration present in the plasma after approximately forty minutes. The rate of accumulation of radioactive phosphorus, probably in the form of phosphate, in the anterior chamber is much less rapid than that for sodium and chloride. The implication of these findings with respect to formation of whole aqueous is commented on.

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CARCINOMA OF THE LIMBUS

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Primary carcinoma of the limbus is relatively uncommon. The following case is significant and of interest because (1) it illustrates a similarity to cases already reported, (2) the only sign remaining after treatment was a small conjunctival scar, and (3) no recurrence, metastases or complication has resulted at the time of writing.

REPORT OF A CASE

A white man aged 47 was admitted to Bellevue Hospital on Oct. 9, 1940 complaining of itching and tearing of the left eye. The family and the past history were essentially unimportant except to reveal the fact that the patient had been punched in this eye about seven years before. Examination showed that he was underweight, and the apex of the right lung contained an area of old, healed tuberculosis. Auricular fibrillation was present, but there were no signs of decompensation. The Wassermann test of the blood was negative. Examination of the blood showed 6,000,000 erythrocytes, with 85 per cent hemoglobin and 8,400 leukocytes. The liver and the spleen were not palpable, and no pathologic reflexes were elicited.

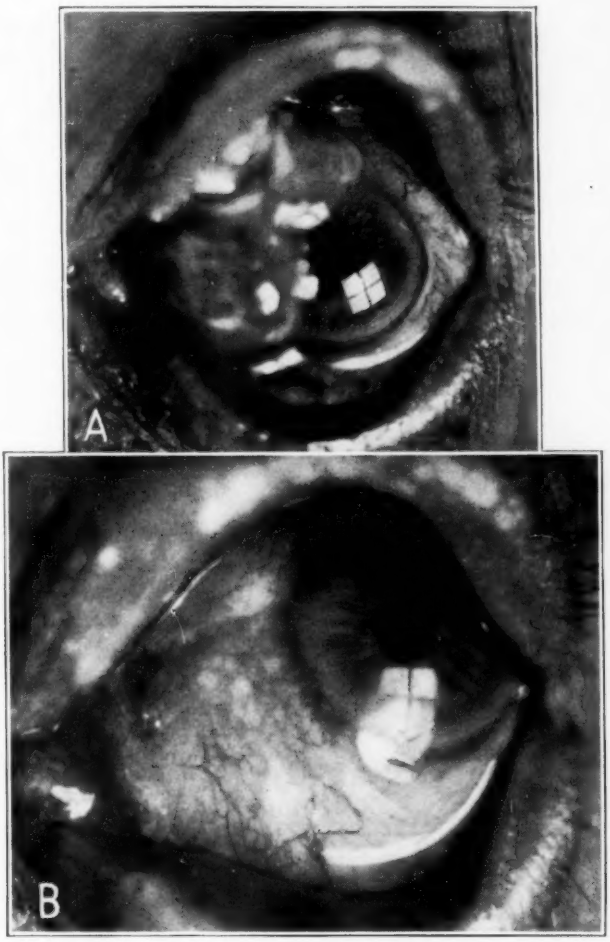
The right eye showed no diseased condition, and the vision was 20/20 uncorrected. The left eye presented a tumor at the nasal aspect of the limbus, extending to but not including the caruncle. The mass measured about 14 mm. in length and 10 mm. in width and was elevated about 4 mm. above the level of the limbus. It was firm and pink and exhibited a few small areas of erosion over the crest, these areas appearing as grayish plaques. The medial one third of the cornea was obscured by the growth, and at the upper limbus this reached the midline of the cornea. The anterior chamber was clear and deep. The pupil reacted to light and in accommodation, and the extraocular muscles were normal. The lens contained a few anterior cortical water clefts. The tension of the affected eye was 27 (Schiøtz), while that of the right eye was 25. The fundus showed slight tortuosity of vessels, with a narrowing of arteries. There was no enlargement of the submaxillary, submental or cervical glands. No metastatic involvement of the orbits, skull or chest was present. The vision in the left eye was 20/40 uncorrected.

A diagnosis of epithelioma of the limbus was made, and one week after admission the mass was removed surgically. One per cent pontocaine hydrochloride solution was instilled as a local anesthetic. The tumor dissected readily and cleanly. To minimize the possibility that any cells would be spread, it was not grasped with an instrument. It did not invade the cornea or the sclera. The portion of cornea which had been overlapped was curetted with a sharp knife, cauterized with trichloroacetic acid and then covered by a conjunctival flap pulled down from above. This flap separated in about one week and left a clear cornea.

Pathologic examination revealed the presence of squamous cells both clumped and spread diffusely. The cells were moderately anaplastic, and a number of

mitotic figures were present. Typical epithelial pearls were identified. The pathologic diagnosis of squamous cell epithelioma confirmed the clinical diagnosis.

About two weeks after the operation some superficial roentgen ray treatment was given, and the following week a radium mold was applied and a dose of 2,000 milligram hours given. Radium dermatitis developed but subsided with the applica-



A, the eye Oct. 10, 1940. *B*, the eye Jan. 18, 1941.

tion of boric acid ointment. At the time of writing, about seven months after operation, the eye is quiet and shows no evidence of previous involvement except for a slight conjunctival scar. The cornea is clear, the lens shows no changes and the vision is unimpaired.

Many characteristics of this case correspond to those of other cases reported. The old injury may not have been a factor. The site was

the favorite one. The tumor was mild in malignancy, with no invasion of neighboring lymph glands. Such tumors occur more frequently in men and seldom before the age of 40. Multiple lesions are rare.

If treatment is begun early, the prognosis is good. A review of the literature shows that surgical intervention and radium therapy, singly or combined, have given the best results. Neglect may lead to evisceration or exenteration. I realize that this patient cannot be listed as cured, but I hope to follow him over a period of years, keeping in mind the possibility of radiation cataract.

SUMMARY

The case is reported of a white man aged 47 who complained of itching and running of the left eye for two months and was not aware of any growth, although examination showed extending from the nasal limbus a rather firm, irregular, pink and slightly ulcerated tumor measuring 14 by 10 by 4 mm. The treatment consisted of surgical removal of the tumor, cauterization of the involved portion of the cornea with trichloroacetic acid and covering of this portion with a conjunctival flap. Postoperatively, one roentgen ray treatment was given and 2,000 milligram hours of radium therapy used. Pathologic examination confirmed the diagnosis of squamous cell carcinoma. There has been no recurrence or metastasis in seven months. A similarity is noted to many of the 313 cases reviewed in the literature.

1502 Park Building.

TREATMENT OF EXPERIMENTAL BACILLUS PYOCYANEUS ULCER OF CORNEA WITH SULFAPYRIDINE

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REVIEW OF THE LITERATURE

Infection of the cornea by Bacillus pyocyaneus is relatively rare, only 64 cases having been reported in the literature. Case reports have been collected by several authors, but the collections of Mauersberg,[1] Jacobi [2] and Morelli [3] have been the most thorough. In 1910 Mauersberg collected 24 cases, to which he added 1 of his own. Two years later Jacobi reviewed the literature and added 4 cases that had occurred during the intervening period. In 1922 Morelli, after describing 3 cases, tabulated 38 found in the literature. There apparently was a duplication in this report, for he attributed identical cases to McNab [4] and to Angus, whereas Angus is the given name of McNab. Of the cases recorded, 9 had occurred since Jacobi's paper was published, but Axenfeld's [5] case, described in 1917, was omitted. As no complete report has been published since Morelli's article appeared, the 23 cases that have been described in the literature since 1922 are presented in table 1.[6]

In spite of its infrequent occurrence, B. pyocyaneus ulcer of the cornea is an important disease, because it usually runs a severe and rapid course and has an unfavorable termination. B. pyocyaneus is perhaps

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Candidate's thesis for admission to the American Ophthalmological Society.

The sulfapyridine sodium was donated by Merck & Co., Inc., Rahway, N. J.

This investigation was aided by a grant from the Hendricks Research Fund.

From the Department of Ophthalmology, Syracuse University College of Medicine.

1. Mauersberg: Ztschr. f. Augenh. **24**:299, 1910.

2. Jacobi, P.: Ueber einen Fall von Ulcus corneae hervorgerufen durch den Bacillus pyocyaneus, Thesis, Heidelberg, G. Geier, 1912.

3. Morelli, E.: Arch. di ottal. **29**:285, 1922.

4. This name occurs in the literature both as McNab and as MacNab.

5. Axenfeld, T.: Deutsche med. Wchnschr. **43**:1182, 1917.

6. One case (Piretti and Ledesma) is included in which the infecting organism was identified as Pseudomonas chlororaphis, which differs from Pseudomonas aeruginosa (B. pyocyaneus) in certain cultural characteristics (Bergey, D. H., and others: Bergey's Manual of Determinative Bacteriology, ed. 5, Baltimore, Williams & Wilkins Company, 1939, p. 128).

the most virulent organism that attacks the cornea.[7] Although most strains are highly pathogenic, they may vary in virulence, and the severity of the infection will vary accordingly.[8] Occasionally a mild infection occurs, but, as a rule, B. pyocyaneus produces a rapidly destructive lesion of the cornea, involving the lids and the anterior segment of the globe. According to Salani,[9] four characteristics of B. pyocyaneus keratitis are (1) the rapid course; (2) the extent of corneal infiltration, which often includes the whole cornea; (3) the amount of

TABLE 1.—*Cases of Bacillus Pyocyaneus Keratitis in the Literature Since 1922*

Year	Author	No. of Cases	Initial Injury to Cornea	Outcome	Comment
1926	Bolesch [10]	1	Slight trauma	Exenteration	
1926	Šafář [12a]	1	Iron splinter	Enucleation	
1926	Schneider [8a]	3	Egg shell	Evisceration	
			Iron splinter	Phthisis bulbi	
			Sand	Enucleation	Panophthalmitis
1927	Garretson and Cosgrove [11]	7	Foreign body, 6	Vision 1/10, <1/10, 6/10, <1/10, 20/20, 20/30	
			Dust, 1	Vision, none	Rupture of cornea
1927	Ohm, J.: Klin. Monatsbl. f. Augenh. **78**: 62, 1927	1	Drying of cornea	Exenteration	
1929	Howard, H. J., and James, W. M.: J. A. M. A. **93**: 1783 (Dec. 7) 1929	2	Not stated	Right, lost Left, healed	
1934	Giannini [10a]	1	Denied injury	Vision, 1/10	
1935	Shearer, H. A.: Arch. Ophth. **13**: 447 (March) 1935	3	Foreign body	Enucleation Enucleation Enucleation	Panophthalmitis
1935	Lanou [14a]	2	Gravel Foreign body	Evisceration Evisceration	Panophthalmitis
1938	Piretti F., and Ledesma, C. H.: Cong. argent. de oftal. (1936) **2**: 607, 1938	1*	No evidence of injury	Total leukoma	Rupture of cornea
1939	Guyton [27]	1	No history of injury	Enucleation	Panophthalmitis

* Organism identified as Pseudomonas chlororaphis.

hypopyon, which is likely to be large, and (4) the mucous consistency of the pus covering the ulcer and the color, which is often greenish.

The infection may appear in the form of a progressive ulcer or, less frequently, of a ring abscess. Of the reported cases collected by Morelli,

7. Herrnheiser, J.: Ztschr. f. Heilk. **14**:41 and 159, 1893; cited by Axenfeld T.: Bacteriology of the Eye, translated by A. McNab, New York, William Wood & Company, 1908, p. 311. Browning, S. H., in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 555.

8. (*a*) Schneider, R.: Klin. Monatsbl. f. Augenh. **77**:103, 1926. (*b*) Šafář, K.: Ztschr. f. Augenh. **61**:25, 1927. (*c*) Mauersberg.[1]

9. Salani, C.: Ann. di ottal. **39**:474, 1910.

a ring abscess occurred in 17 per cent. Whether or not it will develop is probably dependent on the virulence of the organism and the resistance of the tissues.[10] Its occurrence is dependent on the toxic reaction of the invading bacteria and does not denote a different form of infection.[8a]

Even in the cases of less severe involvement, vision is usually greatly reduced by the formation of leukoma. More frequently, however, there is complete corneal destruction, resulting in anterior staphyloma or panophthalmitis. Of his cases, Morelli reported loss of the eye in 23, leukoma in 14 and nebula in 1; in 3 the outcome was not stated. Analysis of the cases that have been reported since 1922 shows that in 15 there was complete loss of vision; in 12 of these the globe was enucleated or eviscerated, generally because of impending or actual panophthalmitis. In 5 eyes vision was reduced to an extremely low degree, whereas in 2 there was little or no loss of vision; in 1 the final degree of vision was not stated. In Garretson and Cosgrove's [11] cases, the favorable results reported were probably due to the fact that the organism was not exceedingly virulent. Using the same strain, Jackson and Hartman [12] were unable to produce infection in the rabbit's cornea except by making intracorneal injections.

Although many methods have been utilized in combating the infection, as a rule they have proved ineffective.[13] It is probable that the degree of virulence of the organism is more responsible for the outcome than is any particular form of therapy.[14] The two local measures considered most efficacious appear to be cauterization and the Saemisch section,[15] but these, as well as the use of local antiseptics, have generally proved unsatisfactory.[16]

The ineffectiveness of local therapy is demonstrated by Šafář's [8b] experiments on rabbits, in which all measures failed to check the progress of the infection after the first clinical appearance of the corneal infiltration. These measures included irrigation with a 25 per cent solution of mild protein silver or a 2 per cent solution of acriflavine hydrochloride, application of boric acid powder, subconjunctival injection of an

10. (*a*) Giannini, D.: Ann. di ottal. e clin. ocul. **62**:869, 1934. (*b*) Schneider.[8a] (*c*) Šafář.[8b]

11. Garretson, W. T., and Cosgrove, K. W.: Ulceration of Cornea Due to Bacillus Pyocyaneus, J. A. M. A. **88**:700 (March 5) 1927.

12. Jackson, E., and Hartman, F. W.: J. Lab. & Clin. Med. **12**:442, 1927.

13. (*a*) Šafář, K.: Ztschr. f. Augenh. **58**:269, 1926. (*b*) Lamb, H. D., and Calhoun, J. G.: Am. J. Ophth. **33**:257, 1916. (*c*) Giannini.[10a]

14. (*a*) Lanou, W. W.: Am. J. Ophth. **18**:950, 1935. (*b*) Mauersberg.[1] (*c*) Šafář.[8b]

15. Pagenstecher, H. E.: Arch. f. Ophth. **79**:132, 1911. McNab, A.: Ophth. Rev. **23**:65, 1904. Jacobi.[2] Morelli.[3] Garretson and Cosgrove.[11]

16. Šafář.[8b] Giannini.[10a]

iodine solution and trepanation of the infiltration. Furthermore, infection was not prevented nor was its course altered if immediately after inoculation the eye was irrigated for from ten to fifteen minutes with a 25 per cent solution of mild protein silver, or if it was exposed for five minutes to the rays of short wave light. On the other hand, an ulcer did not develop if boric acid powder was immediately dusted on the abrasion. Voss [17] and Passow,[18] among others, had commented on the action of boric acid on B. pyocyaneus, whereas Bolesch [19] in experiments on rabbits found that the drug caused a diminution of the conjunctival discharge but did not curb the corneal destruction.

On the basis of clinical and experimental evidence, Šafář [8b] affirmed that local therapy begun after the appearance of corneal infiltration is not generally successful. Acceptance of his concept of pathogenesis would explain the inefficacy of local treatment. In a rabbit's eye enucleated thirty-two hours after inoculation he demonstrated the presence of bacilli in normal corneal tissue often far removed from the site of inoculation.[13a] Šafář was not the first to call attention to such migration of B. pyocyaneus, for both de Berardinis [20] and Löhlein [21] had previously demonstrated it. Šafář's [13a] interpretation was that the organisms progress actively in the lymphatic spaces of normal corneal tissue. He contended that they multiply rapidly at the point of entry, propagate vigorously in the normal parenchyma and produce destruction principally by the formation of endotoxins and exotoxins. If this concept is true, it explains the rapid and malignant course of B. pyocyaneus infection of the cornea and the unsatisfactory results that attend local therapy. By the time treatment is instituted, the organisms, having already invaded the normal portion of cornea, are inaccessible to whatever measures are applied.

From what has been said, it would seem that for treatment to be effective, measures that will act with potency and rapidity against the organisms within the corneal stroma must be used. These measures include immunization, stimulation of the defense mechanism by foreign protein therapy and direct destruction of the organisms by chemotherapy. Both active and passive immunologic treatment are impractical because of the relative infrequency of B. pyocyaneus infection and the former because of the time element. Giannini [10a] cited some evidence of the effectiveness of foreign protein therapy, and it is surprising that this form of treatment has not been used more widely.

17. Voss, O.: Veröffentl. a. d. Geb. d. Mil.-San.-Wes. **33**:1, 1906.
18. Passow, A.: Deutsche med. Wchnschr. **49**:953, 1923.
19. Bolesch: Ztschr. f. Augenh. **58**:240, 1926.
20. de Berardinis, D.: Ann. di ottal. **32**:789, 1903.
21. Löhlein, W.: Arch. f. Augenh. **96**:265, 1925.

SULFANILAMIDE AND ITS DERIVATIVES

There appears to be an ever widening applicability of sulfanilamide and its derivatives as their efficacy against more types of organisms is demonstrated. Although recent literature gives them increasing attention, the reports contain little experimental or clinical evidence regarding their use against B. pyocyaneus.

Priority in this respect belongs to Helmholz,[22] who in 1937 reported that the urine of patients receiving sulfanilamide possessed bacteriostatic properties against B. pyocyaneus. Shortly after this he and Osterberg [23] concluded that a greater degree of bacteriostasis was obtained when the urine was alkaline than when it was acid. Using urine cultures, Long and Bliss [24] confirmed the bacteriostatic power of sulfanilamide against B. pyocyaneus in experiments in vitro. However, these writers expressed the belief that the reaction of the urine was unimportant. More recently Helmholz,[25] in investigating the bactericidal effect of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-4-methyl-thiazole) in urinary infections, found that the former drug was much more effective. In equal concentrations (150 mg. per hundred cubic centimeters) of the free drug, sulfathiazole rapidly destroyed the organisms, whereas sulfamethylthiazole allowed them to attain a luxuriant growth. In further studies with sulfathiazole, Helmholz and Larson [26] reported that B. pyocyaneus was the most resistant of the bacteria usually found in urinary infections.

The investigations of Helmholz and of Long and Bliss would seem to substantiate the efficacy of sulfanilamide against B. pyocyaneus in urine; however, urine attains an unusually high concentration of the drug. Cooper, Gross and Lewis [27] reported that both sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) were ineffective in the treatment of experimental peritonitis in mice.

Soon after Helmholz described his first investigation, Herrold [28] reported the cure with sulfanilamide of 2 patients suffering from genitourinary infection due to B. pyocyaneus. Some time later Banerji [29]

22. Helmholz, H. F.: Proc. Staff Meet., Mayo Clin. **12**:244, 1937.

23. Helmholz, H. F., and Osterberg, A. E.: Proc. Staff Meet., Mayo Clin. **12**:377, 1937. Helmholz, H. F.: Comparison of Mandelic Acid and Sulfanilamide as Urinary Antiseptics, J. A. M. A. **109**:1039 (Sept. 25) 1937.

24. Long, O. H., and Bliss, E. A.: South. M. J. **31**:308, 1938.

25. Helmholz, H. F.: Proc. Staff Meet., Mayo Clin. **15**:65, 1940.

26. Helmholz, H. F., and Larson, N.: Proc. Staff Meet., Mayo Clin. **15**:651, 1940.

27. Cooper, F. B.; Gross, P., and Lewis, M.: Proc. Soc. Exper. Biol. & Med. **40**:34, 1939.

28. Herrold, R. D.: Urol. & Cutan. Rev. **41**:468, 1937.

29. Banerji, K. G.: Indian J. Pediat. **5**:188, 1938.

reported the recovery of a child with urinary infection treated with methenamine and "prontosil" (probably the original prontosil, a hydrochloride of 4-sulfamido-2',4'-diaminoazobenzene). Three cases of septicemia have been published, in all of which the outcome was favorable. Soeters [30] described the case of an infant with septicemia complicating infection of the perineum and vulva successfully treated with azosulfamide and blood transfusions. Stewart and Bates [31] reported the recovery of a patient in ten days with sulfanilamide, and Kolmer [32] cited a favorable outcome in a child who received azosulfamide. In this case the blood culture, which showed eighty-two colonies per cubic centimeter, became sterile within four days.[33] Alport and Ghaliougui [34] recorded a case of pyelocystitis and 1 of hepatic abscess. In the former the patient was treated successfully with sulfanilamide after all other measures had failed. In the latter a hepatic abscess caused by the ameba had become secondarily infected with B. pyocyaneus. This patient recovered with aspirations of the abscess and the use of sulfanilamide after sulfapyridine had proved unsuccessful. Schein [35] reported a favorable outcome with administration of sulfanilamide to a patient suffering from osteomyelitis of the spine, and Wise and Musser [36] recorded the recovery of 4 patients with meningitis treated with sulfanilamide and repeated lumbar punctures. Guyton [37] used sulfanilamide after almost the entire cornea was involved with a rapidly progressive B. pyocyaneus ulcer. After the institution of chemotherapy, the ulcer progressed but little, but the drug had to be discontinued because of acute hemolytic anemia. The local application of sulfanilamide had no appreciable effect on the infection. McKeown [38] used sulfathiazole in treating a patient with endophthalmitis following an intraocular operation. Although the inflammation subsided rapidly, the globe atrophied and enucleation became necessary.

Kolmer [32] concluded that sulfanilamide is "worthy of use" in the treatment of B. pyocyaneus infections. He based his conclusions partly

30. Soeters, J. M.: Maandschr. v. kindergeneesk. **7**:74, 1937.

31. Stewart, W., and Bates, T.: Lancet **1**:820, 1939.

32. Kolmer, J. A.: Progress in Chemotherapy of Bacterial and Other Diseases, with Special Reference to Prontosils, Sulfanilamide and Sulfapyridine, Arch. Int. Med. **65**:671 (April) 1940.

33. Kolmer, J. A.: Personal communication to the author.

34. Alport, A. C., and Ghaliougui, P.: Lancet **2**:1062, 1939.

35. Schein, A. J.: Bacillus Pyocyaneus Osteomyelitis of Spine: Report of Case of Successful Treatment with Sulfanilamide, Arch. Surg. **41**:740 (Sept.) 1940.

36. Wise, R. A., and Musser, J. H.: New Orleans M. & S. J. **92**:145, 1939.

37. Guyton, J. S.: Am. J. Ophth. **22**:833, 1939; personal communication to the author.

38. McKeown, H. S.: Personal communication to the author.

on the results of Cooper and his associates. However, there seems to have been a misinterpretation, for he classified their findings as demonstrating that the drugs proved effective, when as a matter of fact they did not except against small lethal doses.

The pharmacologic action of sulfanilamide and its derivatives has not been determined definitely,[39] nor is it known how much of the action is quantitative and how much qualitative.[40] However, there is apparently, at least, some specificity of action.[40] One peculiarity is that some strains of the same organism are usually more resistant than others.[41] An important action of the compounds is their rapid absorption and penetration into the various tissues and body fluids, as demonstrated by Marshall and his associates [42] and later by Engelfried,[43] Birkhaug [44] and others.

Penetrability of Ocular Tissues and Fluids.—Rambo [45] was the first to demonstrate the presence in the eye of any of these drugs. He detected sulfanilamide in the ocular fluids and the lens of a rabbit that had received the drug orally. Some time later Guyton [37] recovered the drug from the aqueous humor, and Mengel [46] found it in both the aqueous humor and the vitreous humor of patients receiving sulfanilamide orally. At about the same time Scardaccione [47] made quantitative studies on the diffusion of the drug into the aqueous humor, while Venco [48] recovered it from the ocular fluid of rabbits and from the lacrimal secretion of human beings. Bellows and Chinn [49] likewise found sulfanilamide in the tears of patients who received the drug orally. Pinkhof [50] was the first to report the permeation of sulfapyridine into the ocular fluids. After oral administration of the drug to rabbits, its concentration in the lacrimal fluid closely approximated that in the blood, whereas the concentration in the ocular fluids was about one fourth as much.

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39. Long, P. H., and Bliss, E. A.: Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939.

40. Marshall, E. K., Jr.: Physiol. Rev. **19**:240, 1939.

41. Marshall, E. K., Jr.: Science **91**:345, 1940.

42. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: J. Pharmacol. & Exper. Therap. **61**:196, 1937.

43. Engelfried, J. J.: Univ. Hosp. Bull., Ann Arbor **4**:4, 1938.

44. Birkhaug, K. E.: Proc. Soc. Exper. Biol. & Med. **42**:270, 1939.

45. Rambo, V. C.: Am. J. Ophth. **21**:739, 1938.

46. Mengel, W. G.: Determination of Sulfanilamide in Aqueous and Vitreous After Conjunctival and Oral Administration, Arch. Ophth. **22**:406 (Sept.) 1939.

47. Scardaccione, cited by Cavara, V.: Boll. d'ocul. **18**:597, 1939.

48. Venco, L.: Ann. di ottal. e clin. ocul. **67**:30, 1939.

49. Bellows, J. G., and Chinn, H.: Distribution of Sulfanilamide in Eye, J. A. M. A. **112**:2023 (May 20) 1939.

50. Pinkhof, J.: Nederl. tijdschr. v. geneesk. **83**:3711, 1939.

That sulfanilamide and sulfapyridine penetrate into the ocular tissues as well as into the fluids has been established. Bellows and Chinn,[51] experimenting on dogs, found that the permeation is rapid and widespread after a single large dose (0.2 Gm. per kilogram). On the other hand, these observers have recently reported that only traces of the drug appear in the fluids and avascular tissues of the eye after the administration of sulfathiazole under similar conditions.[52]

According to these investigators, after the administration of sulfanilamide and sulfapyridine the concentration curve of the ocular constituents followed that of the blood, although usually at a lower level. However, the values for the aqueous and particularly for the cornea were relatively high. Meyer and his co-workers [53] made similar observations. Moreover, the latter investigators reported that in rabbits receiving sulfapyridine orally the concentration of the drug in the cornea equaled or exceeded that attained by the blood after a period of seven hours. In vitro experiments showed that the cornea attained a higher concentration with sulfanilamide than with sulfapyridine.

Bellows and Chinn [51] found that the maximum concentration of the drug in the ocular tissues and fluids was reached in about four hours with sulfapyridine and in about six hours with sulfanilamide and that both drugs were still present in all components twenty-four hours after they were administered. Therapeutic doses produced much lower levels, but the concentrations in the blood, although considerably lower than those secured in human beings receiving a proportional dose, remained fairly constant. Little difference could be detected in the concentration of drug in the ocular tissues and fluids whether sulfanilamide was administered four times daily or twice daily.

The local application of sulfanilamide and sulfapyridine produces a lower concentration in the ocular tissues and fluids than is obtained after oral administration. Bellows and Chinn [49] reported that the application of sulfanilamide powder to the cornea and conjunctiva elicited a positive reaction in the subconjunctival tissue and the corneal stroma but that none could be detected in the ocular fluids. These investigators reported that the concentration of the drug in the aqueous humor after subconjunctival injection of 1 cc. of a saturated solution was much lower than after oral administration. Likewise Guyton [37] and Mengel [46] found after instillation into the conjunctival sac a negligible amount in the

51. Chinn, H., and Bellows, J. G.: J. Lab. & Clin. Med. **25**:735, 1940. Bellows and Chinn.[49]

52. Bellows, J. G., and Chinn, H.: Penetration of Sulfathiazole in Eye, Arch. Ophth. **25**:294 (Feb.) 1941.

53. Meyer, K.; Bloch, H. S., and Chamberlain, W. P., Jr.: Am. J. Ophth. **24**:60, 1941.

aqueous humor as compared with that appearing after oral administration. Pinkhof [50] obtained similar results with sulfapyridine. None of the drug was recovered from the ocular fluids after application of a paste of sulfapyridine to the conjunctiva, and only a small amount was found in the aqueous humor after the subconjunctival injection of a 6 per cent suspension of the drug.

Variability in Permeation.—Both sulfanilamide and sulfapyridine show considerable variability in their permeation, the permeation not necessarily being proportional to the dose.[39] Not infrequently the concentration of the drug in the blood of a patient remains low in spite of large doses. Moreover, the concentration may vary in different patients after identical doses administered under similar conditions.[39] This variability is even greater in animals, particularly in rabbits and guinea pigs.[39] McMahon [54] found wide variations in rabbits receiving similar doses of sulfanilamide, and Lee and his co-workers [55] have shown that individual pregnant rabbits displayed marked variations under standard conditions. Long and Feinstone,[56] Marshall and his associates [57] and Chinn and Bellows [51] have demonstrated that sulfapyridine is irregularly absorbed and that its concentration is more variable than is that of sulfanilamide. Long and Bliss [39] reported that frequently, even after prolonged intensive therapy, free sulfapyridine can be found in the blood only in traces. These workers concluded that the absorption, distribution, conjugation and excretion of sulfapyridine are definitely more irregular and capricious than those of sulfanilamide and that one cannot depend on the former drug to reach the affected tissues as one can depend on sulfanilamide. Although sulfapyridine is less readily absorbed, its concentration in the blood of animals is better maintained than is that of sulfanilamide. This is an important factor and may account for the better therapeutic results attained in certain experimental infections.[39]

Sulfapyridine Sodium.—In 1938 the monosodium salt of sulfapyridine was introduced in the effort to overcome the insolubility and difficult absorption of sulfapyridine.[57] Powell and Chen [58] have recently reviewed the literature on sulfapyridine sodium and have published the results of their investigations.

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54. McMahon, B. J.: Influence of Sulfanilamide on Infected Sinuses of Rabbits: Chemical and Microscopic Studies, Arch. Otolaryng. **28**:222 (Aug.) 1938.

55. Lee, H. M.; Anderson, R. C., and Chen, K. K.: Proc. Soc. Exper. Biol. & Med. **38**:366, 1938.

56. Long, P. H., and Feinstone, W. H.: Proc. Soc. Exper. Biol. & Med. **39**:486, 1938.

57. Marshall, E. K., Jr.; Bratton, A. C., and Litchfield, J. T., Jr.: Science **88**:597, 1938.

58. Powell, H. M., and Chen, K. K.: J. Indiana M. A. **33**:503, 1940.

Certain salient features are characteristic of this drug. Thus, it is more rapidly and completely absorbed and more rapidly eliminated than is sulfapyridine.[57] When injected intravenously, it can be detected in the blood in high concentrations almost immediately.[59] Although after oral administration its absorption is considerably slower, Bullowa and his associates [60] found that in human beings concentrations were often as good as those obtained after intravenous injection. Therapeutic levels were attained as soon as thirty-five minutes after a single dose, and maximum concentrations were reached in from two and one-half to four hours, depending on the size of the dose.

Sulfapyridine sodium is decidedly more toxic than sulfapyridine.[61] Molitor and Robinson [62] found that the oral administration of a 10 per cent aqueous solution of sulfapyridine sodium produced severe gastric irritation in rats, rabbits and monkeys and that there was a marked tendency to the formation of calculi. Later, Antopol and Robinson [63] reported that calculi formed with smaller doses of sulfapyridine sodium than of sulfapyridine and that the former produced degenerative changes in the kidneys and in isolated instances caused acute diffuse gastritis in rabbits. On the other hand, Powell and Chen [58] reported that irritation did not occur when a 10 per cent solution was instilled into a rabbit's conjunctival sac and that no pathologic conditions were found in dogs which had received daily oral doses of from 0.25 to 0.5 Gm. per kilogram for twenty-four days. Many other investigators have administered the drug to animals routinely by the oral route without apparent ill effect. Bullowa, Ratish and their associates [64] reported that sulfapyridine sodium was well tolerated after oral administration and that in no patient did gastroenteritis or colitis occur because of its alkalinity.

Powell and Chen [58] found that sulfapyridine sodium administered orally to mice proved three times as effective as sulfapyridine against streptococci, meningococci of type III and staphylococci.

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59. Brown, W. H.; Thornton, W. B., and Wilson, J. S.: J. Clin. Investigation **18**:803, 1939. Powell and Chen.[58]

60. Bullowa, J. G. M.; Ratish, H. D.; Davidson, A., and Lebair, C.: New York State J. Med. **40**:1450, 1940.

61. Toomey, J. A.; Reichle, H. S., and Takacs, W. S.: J. Pediat. **16**:179, 1940. Powell and Chen.[58]

62. Molitor, H., and Robinson, H.: Proc. Soc. Exper. Biol. & Med. **41**:409, 1939.

63. Antopol, W., and Robinson, H. J.: Pathologic and Histologic Changes Following Oral Administration of Sulfapyridine, with Short Note on Sodium Sulfapyridine, Arch. Path. **29**:67 (Jan.) 1940.

64. Ratish, H. D.; Davidson, A., and Bullowa, J. G. M.: J. Pharmacol. & Exper. Therap. **69**:365, 1940. Bullowa and others.[60]

EXPERIMENTS

In undertaking the following experiments the purpose was to ascertain whether or not in rabbits the oral administration of sulfapyridine would prevent or favorably affect infection of the cornea produced by B. pyocyaneus. It was necessary, however, first to determine the antibacterial action of the drug against the organism in vitro.

IN VITRO EXPERIMENTS

The bactericidal and bacteriostatic effects of a concentration of sulfapyridine sodium of 10 mg. per hundred cubic centimeters were studied on three strains of B. pyocyaneus contributed by Dr. Phillips Thygeson from the Institute of Ophthalmology, New York. These strains are designated as A, B and C. A and B were stock cultures, whereas C was recovered from the eye of a patient suffering from keratitis sicca. As described further on, two distinct types of colonies developed from strain A on blood agar plates. These are designated as A1 and A2. Although each produced a typical experimental corneal ulcer, that of A1 was the severer, and because of this it was used later for the animal experiments. Strain B was apparently less hardy than A, and, although corneal inoculation produced an ulcer, its virulence and pigment production were soon lost, and they were revived with some difficulty by animal passage. The virulence of strain C was decidedly low. Only a trace of pyocyanin was found, and experimental inoculation produced an unusually mild ulcer which healed in a few days with little progression. Its virulence and pigment production were increased by passage through a guinea pig, and as a result a severe experimental ulcer was produced. However, in twenty-four hours the strain had returned to its previous state and could not be revived, despite repeated passage through guinea pigs.

Methods.[65]—Infusion-free broth with dextrose as prepared by Wadsworth and Brown[66] was used throughout. To 500 cc. of broth 0.05 Gm. of sulfapyridine sodium was added, and the mixture was heated slightly to aid in dissolving the drug. The solution (a concentration of 10 mg. per hundred cubic centimeters) was then distributed in 5 cc. quantities in sterile plugged test tubes. Broth to which no drug had been added was distributed in control tubes. All the tubes were sterilized in the autoclave at 15 pounds (7 Kg.) of pressure for fifteen minutes.

One drop of a broth culture of B. pyocyaneus which had been incubated at 37 C. for eighteen hours was added to a medication tube and to a control tube. Subcultures were made at different time intervals with second medication and control tubes. The subcultures were incubated at 37 C. for at least seventy-two hours before the results were recorded.

65. Based on investigations by O. W. Barlow, M.D., Ph.D., director of the Biologic and Research Laboratories, Winthrop Chemical Co., Inc.

66. Wadsworth, A., and Brown, R.: J. Immunol. **32**:467, 1937.

The experiment was repeated three times each with strains A1, A2 and B and twice with strain C. Similar tests were made with sulfanilamide. The results are presented in table 2.

TABLE 2.—*Bacteriostatic Action on B. Pyocaneus in Broth of a 10 Mg. per Hundred Cubic Centimeters Concentration of Sulfapyridine and of Sulfanilamide*

Strain of Organism	Drug	Time Intervals of Transfers in Hours							
		1-5	5	8	24	32	48	56	72
A1	Sulfapyridine	+*	+	—†	—	—	—	—	—
	Control		+	+	+	—	—	—	—
	Sulfapyridine	+	+	—	—	—	—	—	—
	Control		+	—	—	—	—	—	—
	Sulfapyridine	+	+	+	—	—	—	—	—
	Control		+	+	—	—	—	—	—
A2	Sulfapyridine	+	+	—	—	—	—	—	—
	Control		+	+	+	—	—	—	—
	Sulfapyridine	+	+	+	+	—	—	—	—
	Control		+	+	+	—	—	—	—
	Sulfapyridine	+	+	+	—	—	—	—	—
	Control		+	+	—	—	—	—	—
B	Sulfapyridine	+	+	—	—	—	—	—	—
	Control	+	+	+	—	—	—	—	—
	Sulfapyridine	+	—	—	—	—	—	—	—
	Control		+	—	—	—	—	—	—
	Sulfapyridine	+	—	—	—	—	—	—	—
	Control		+	—	—	—	—	—	—
C	Sulfapyridine	+	+	+	+	+	+	+	+
	Control		+	+	+	+	+	+	+
	Sulfapyridine	+	+	+	+	+	+	+	+
	Control		+	+	+	+	+	+	+
A1	Sulfanilamide	+	+	+	—	—	—	—	—
	Control		+	+	—	—	—	—	—
	Sulfanilamide	+	+	+	+	+	+	—	—
	Control		+	+	+	+	+	—	—
A2	Sulfanilamide	+	+	+	+	—	—	—	—
	Control		+	+	+	—	—	—	—
	Sulfanilamide	+	+	+	—	—	—	—	—
	Control		+	+	+	—	—	—	—
B	Sulfanilamide	+	+	—	—	—	—	—	—
	Control		+	—	—	—	—	—	—
	Sulfanilamide	+	—	—	—	—	—	—	—
	Control		—	—	—	—	—	—	—
	Sulfanilamide	+	+	—	—	—	—	—	—
	Control		+	—	—	—	—	—	—
C	Sulfanilamide	+	+	+	+	+	+	+	+
	Control		+	+	+	+	+	+	+
	Sulfanilamide	+	+	+	+	+	+	+	+
	Control		+	+	+	+	+	+	+

* A plus sign indicates growth.
† A minus sign indicates no growth.

Comment.—In these experiments sulfapyridine sodium proved more efficacious than sulfanilamide. The former was effective against strains B, A1 and A2 in that order. As a rule no growth was apparent after the eighth hour, and in only 1 instance was growth evident as late as the twenty-fourth hour. While sulfanilamide proved equally effective against

strain B, it was less potent than sulfapyridine sodium against strains A1 and A2. Both drugs were totally ineffectual against strain C.

Judging from the production of pigment and from the results of experimental corneal inoculation, the virulence of these strains, listed in decreasing order, was A1, A2, B and C. It is interesting to note that the least virulent strain was the most resistant.

IN VIVO EXPERIMENTS

Animals.—Albino rabbits from 6 to 8 months old and weighing from 1,500 to 3,000 Gm. were used in all the experiments. Care was taken to distribute the animals as to weight as evenly as possible through the experimental and the control groups.

B. Pyocyaneus Culture.—The strain used was the one previously designated as A. It had been used successfully at the Institute of Ophthalmology, New York, in producing experimental corneal ulcers in rabbits, and it fulfilled all the cultural characteristics of the organism as defined by Bergey.[67]

Two distinct types of colonies developed on blood agar plates. In one, designated as A1, there were rough, dark green colonies with a flat, granular surface and irregular edges. Sometimes the surface showed lytic areas or crater-like pockets and a metallic sheen. In the other type, A2, the colonies were smooth, dark green and round, with a slightly curved surface and clearcut margins. The two types were isolated, but no further differences in cultural characteristics could be demonstrated. Experimental inoculation showed that the first type usually produced the severer ulcers, and for this reason A1 was used in the animal experiments. During the course of animal experimentation, which was extended for eight months, the ability to produce pyocyanin was lost in 2 instances, and in both the culture failed to produce a satisfactory corneal lesion. Passage through guinea pigs revived the production of pigment and restored the original virulence of the organism. Schneider [8a] concluded that lost virulence can be regained by animal passage but that nonvirulent species are not affected.

Preparation of Culture.—Beef extract broth was used throughout the experiments. Transfer of the culture from the agar slant to the broth was made with a platinum loop. The broth culture was then incubated at 37 C. for twenty-four hours. To avoid contamination, a separate agar slant and broth tube were prepared for each eye inoculated.

Inoculation.—Shortly after 1 drop of a 2 per cent solution of butyn sulfate was instilled, a shallow circular abrasion 1.5 to 2 mm. in diameter was made with a 1.5 mm. dental drill in the central area of the cornea. A cotton swab saturated with a twenty-four hour broth culture of B. pyocyaneus was then applied to the abrasion. The right cornea of 64 rabbits and both corneas of 110 rabbits were used. Extreme care was taken to be sure that all conditions were identical in the control and the experimental animals. As a rule the experiments were carried on in groups of 9 rabbits, approximately one third of which were used as controls. The procedures were completed in one group before they were started in the next.

Observation.—The eyes were examined at least three times within the first twenty-four hours and then twice daily for the remainder of the first week.

67. Bergey and others,[6] p. 126.

During the next two weeks they were usually inspected only once daily, the frequency of inspection depending on the condition. A careful examination was made by two or three observers at least once every day throughout the stage of active infection. At this time the amount of discharge was estimated and the condition of the lids and the anterior ocular segment carefully noted. The size of the corneal lesion was measured, as was the height of the hypopyon when one was present. An attempt was made to ascertain the day of maximum inflammation and to determine the day when healing occurred. It is obvious that both these attempts, as well as the problem of measuring the discharge, offered considerable difficulty. The discharge was classified as scanty, moderate or abundant. The degree of the inflammation was classified as mild, moderately severe or severe.

Unless otherwise specified, the final measurements of the corneal lesion are given as of the seventh day following inoculation. In all the controls, as well as in some of the treated rabbits, the ulcer was still active at this time. For the eyes of these animals the measurements given are those of the ulcer on the seventh day or of the resultant scar, whichever was the larger.

Treatment. — Preliminary experiments in which sulfapyridine sodium was injected into the marginal vein of the ear proved technically unsatisfactory for repeated doses. On the other hand, it was found that sulfapyridine could be administered orally over a long period, in most cases without disturbing the animal, and that the technic was simple and rapid. In preliminary experiments sulfapyridine was used suspended in milk, but this drug was discarded in favor of the soluble sulfapyridine sodium owing to the difficulty in determining accurate doses in suspension and because of the desirability of attaining rapid penetration into the blood and tissues.

In these experiments 12 rabbits died during the course of the treatment, and 5 died within the next few days. Although in the majority of deaths sulfapyridine was probably at least a contributing factor, there was no postmortem evidence that the drug had a deleterious effect on the mucosa of the gastrointestinal tract; nor were uroliths found.

Preparation of Drug and Dosage.—A 30 per cent solution was made by adding 25 Gm. of sulfapyridine sodium to 80.9 cc. of warm water and stirring for a few minutes. This amount was sufficient for two or three days' treatment. The drug was administered twice daily, at 9 a. m. and 5 p. m., and treatment was continued up to six days. The dose for each feeding was 0.5 Gm. per kilogram the first day, 0.35 Gm. per kilogram the second day and 0.25 Gm. per kilogram thereafter.

Technic of Administering Drug.—The rabbit was spread-eagled on its back on an animal rack, a mouth gag was inserted and a catheter (English no. 10) was introduced into the stomach. The solution was slowly injected into the catheter from a 5 cc. syringe. Immediately afterward the apparatus was flushed with 10 cc. of lukewarm tap water to wash down any of the drug that might have adhered to it.

Determination of Drug in the Blood.—The blood of 107 rabbits was analyzed for sulfapyridine by the method of Marshall and Litchfield.[68] Unfortunately,

68. Marshall, E. K., Jr.: J. Biol. Chem. **122**:263, 1937. Marshall, E. K., Jr., and Litchfield, J. T.: Science **88**:85, 1938.

laboratory facilities did not permit routine periodic determinations, although for 39 animals from two to four analyses were made at different intervals. The results proved extremely variable, both for different rabbits and for the same rabbit on different days. The blood was withdrawn from 87 animals six hours after medication, when it was assumed the concentration would be near its peak. Although the values ranged from less than 1 mg. to as high as 31.3 mg. per hundred cubic centimeters, 65 per cent of one hundred and twenty-eight determinations showed the concentration to exceed 3 mg. per hundred cubic centimeters. The blood was withdrawn from 20 rabbits sixteen hours after treatment, and, as anticipated, the value was generally low, that for 76 per cent being less than 3 mg. per hundred cubic centimeters.

In general no relation could be found to exist between the concentration and the course of the inflammation and the outcome. Theoretically the concentration in the blood should be the gage by which to judge the efficacy of the treatment. However, both clinically and in experimental infections, often no such relation exists. As a rule the values are lower for animals than for human beings receiving proportional doses, and it seems probable that the smaller the animal the greater is the dose of the drug necessary to maintain a definite level in the blood.[51] Furthermore, the rabbit is distinguished for its inconsistency in sustaining the level in the blood.[39]

CHARACTERISTICS OF EXPERIMENTAL B. PYOCYANEUS ULCER OF THE RABBIT'S CORNEA

The rabbit's cornea is well adapted for experimental investigation of B. pyocyaneus infection. Most strains have proved highly pathogenic,[8b] and, although a ring abscess may appear in one instance and not in another,[8a] the pathologic picture in the rabbit closely follows that in man.[8b] Inoculation of the rabbit's cornea with the organism produces serious and rapidly progressive keratitis, usually resulting in complete involvement of the cornea within two to four days.

During the course of this study 85 eyes were inoculated as controls. With the exception of 3, in which infection did not result, the site of inoculation became infiltrated within three or four hours. Six hours after inoculation the lesion appeared as a grayish, sharply circumscribed ulcer 1 to 2 mm. in diameter. The ulcer was accompanied by mild hyperemia of the ocular conjunctiva and iris, and occasionally the palpebral conjunctiva and the lid margins were also congested. In a few instances a barely perceptible amount of discharge could be observed at this early stage. During the next twelve hours the margins of the ulcer gradually extended and became less clearly defined, and its color gradually changed to a grayish white. Such a condition, accompanied by an

increasing degree of ocular congestion, was usually found at the end of eighteen hours. At this stage the corneal lesion ordinarily appeared as a dirty white superficial ulcer not larger than 4 mm. in diameter. The adjacent part of the cornea was generally cloudy, and occasionally an infiltration ring was present. Frequently fresh areas of infiltration could be observed, sometimes far removed from the site of inoculation. As a rule it was still too soon to determine whether the infection was to proceed as a progressive ulcer or as a ring abscess. The congestion of the ocular conjunctiva and the iris was decidedly intense, but the anterior chamber remained clear. The palpebral conjunctiva was congested, the lid margins were hyperemic and usually a small amount of grayish white discharge was present.

After the first twenty-four hours the progress of the infection seemed to gain momentum. In 61 eyes (74 per cent) the lesion took the form of

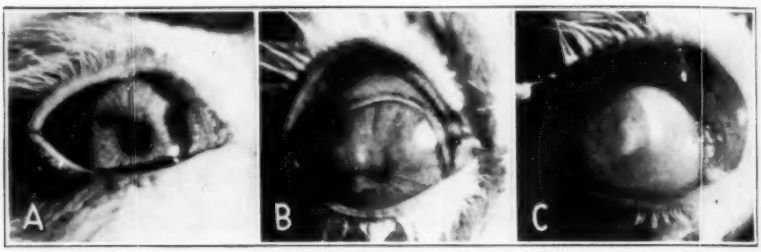

Fig. 1.—Control Eyes: *A*, rabbit 35 six hours after inoculation; *B*, rabbit 48 eighteen hours after inoculation, and *C*, rabbit 48 seventy-two hours after inoculation.

a rapidly progressing ulcer, and in 21 (26 per cent) it was a more or less typical ring abscess. As a rule virtually the entire cornea was invaded within the next day or two, and in 46 eyes (56 per cent) the cornea ruptured. As the infection progressed, the accompanying inflammation increased. Frequently the lids became so edematous as to produce ectropion. The intensity of the conjunctival congestion increased, and the discharge usually increased proportionately with the inflammation, becoming abundant and diminishing only when healing began. In eyes in which the cornea was sufficiently transparent, increased congestion of the iris could be observed. A hypopyon, which could be seen in 66 eyes (80 per cent), usually appeared about the third day and frequently attained considerable size. In most cases the crisis of infection was reached between the third and the fifth day, after which the infection

slowly declined; in a few eyes an exacerbation occurred later. In spite of the almost uniform severity of the infection, there were no instances of panophthalmitis. Vascularization from the limbus was observed as early

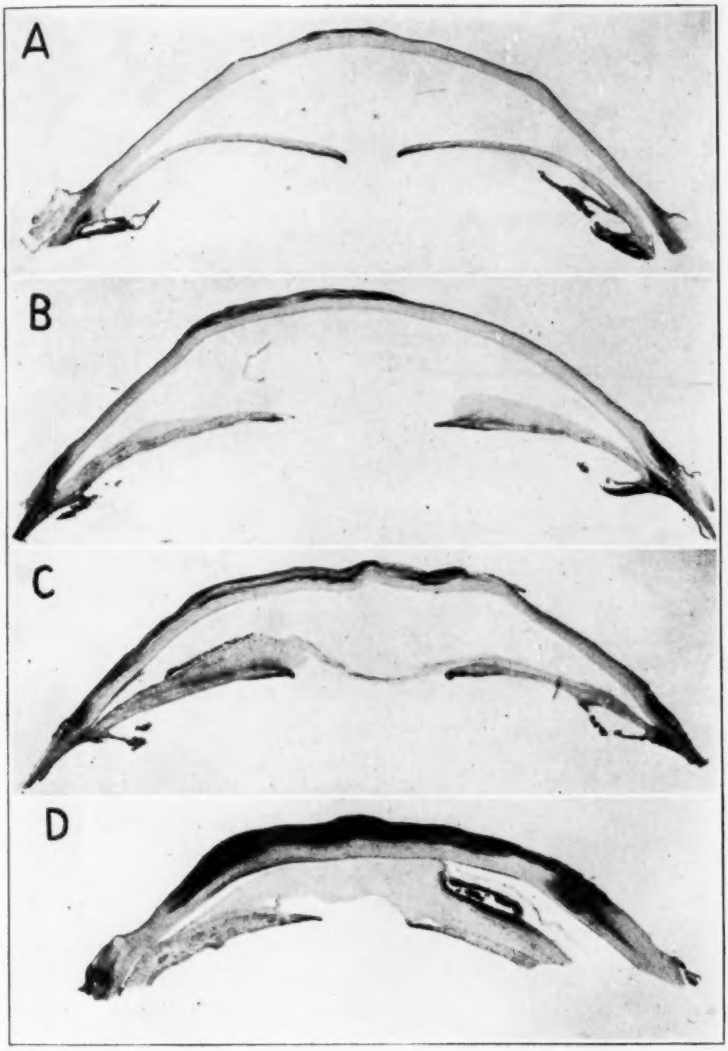

Fig. 2.—Extension of an ulcer, with progressive cellular infiltration of the cornea from the site of the infection and from the limbus, increasing infiltration of the iris and ciliary body and development of a hypopyon (× 6), seventeen hours (*A*), twenty-four hours (*B*), thirty-two hours (*C*) and four days (*D*) after inoculation.

as the third day, but as a rule it did not occur until two or three days later. The duration of inflammation ranged from eight days to three

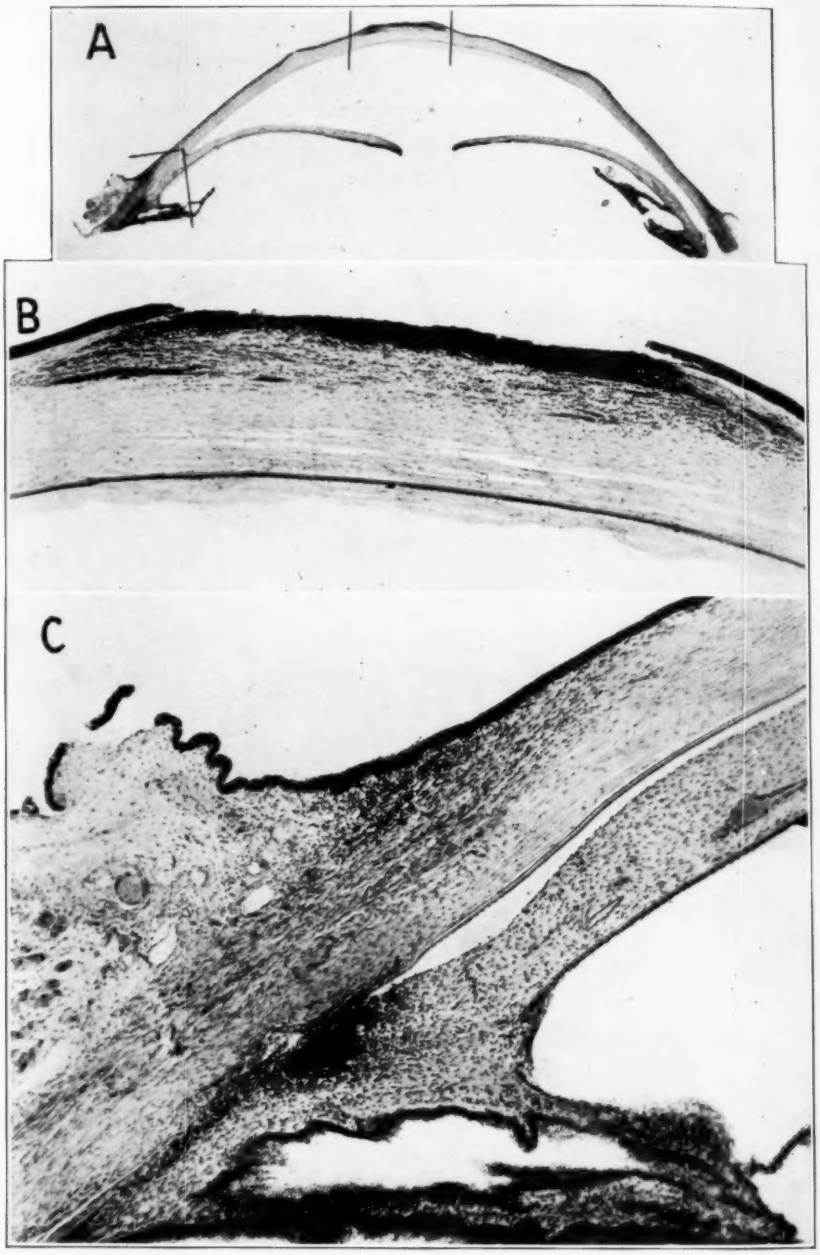

Fig. 3.—*A*, an ulcer seventeen hours after inoculation (× 6). *B*, high power view of the ulcer, showing superficial necrosis and intense cellular infiltration in the anterior lamellas (× 55). *B*, high power view of the limbic region, showing extension of the corneal infiltration toward the ulcer and infiltration of the root of the iris and ciliary body, with the anterior chamber clear (× 55).

weeks, most of the eyes healing in from ten to fourteen days. The resultant scarring was extensive, the entire cornea being involved in 67 eyes (82 per cent). During the course of the inflammation B. pyo-

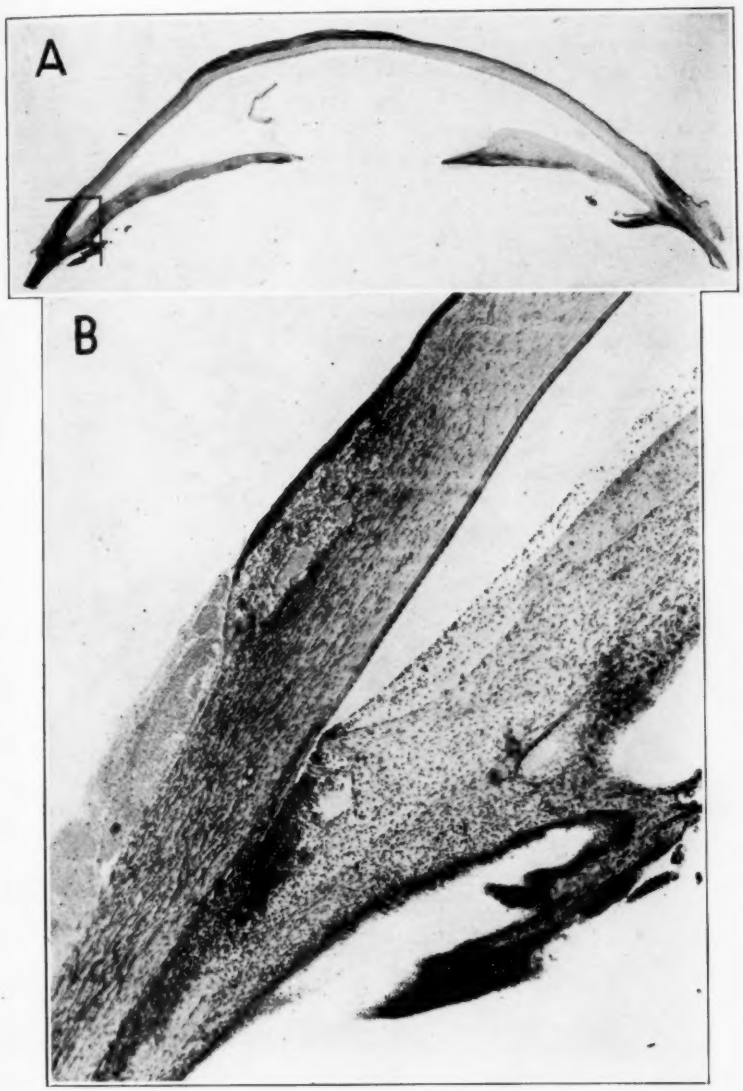

Fig. 4.—*A*, extension of the ulcer twenty-four hours after inoculation (× 6). *B*, high power view of the limbic region, showing increasing infiltration of the cornea from the limbus, more marked infiltration of the iris and the ciliary body and slight exudation in the anterior chamber (× 55).

cyaneus was usually recovered several times, but cultures from 13 eyes (16 per cent) gave consistently negative results.

Figure 1 presents a clinical picture that is fairly typical of an eye six, eighteen and seventy-two hours after inoculation. Figures 2, 3, 4 and 5 demonstrate microscopically the rapidity with which the lesion progresses and the extent of the inflammatory process.

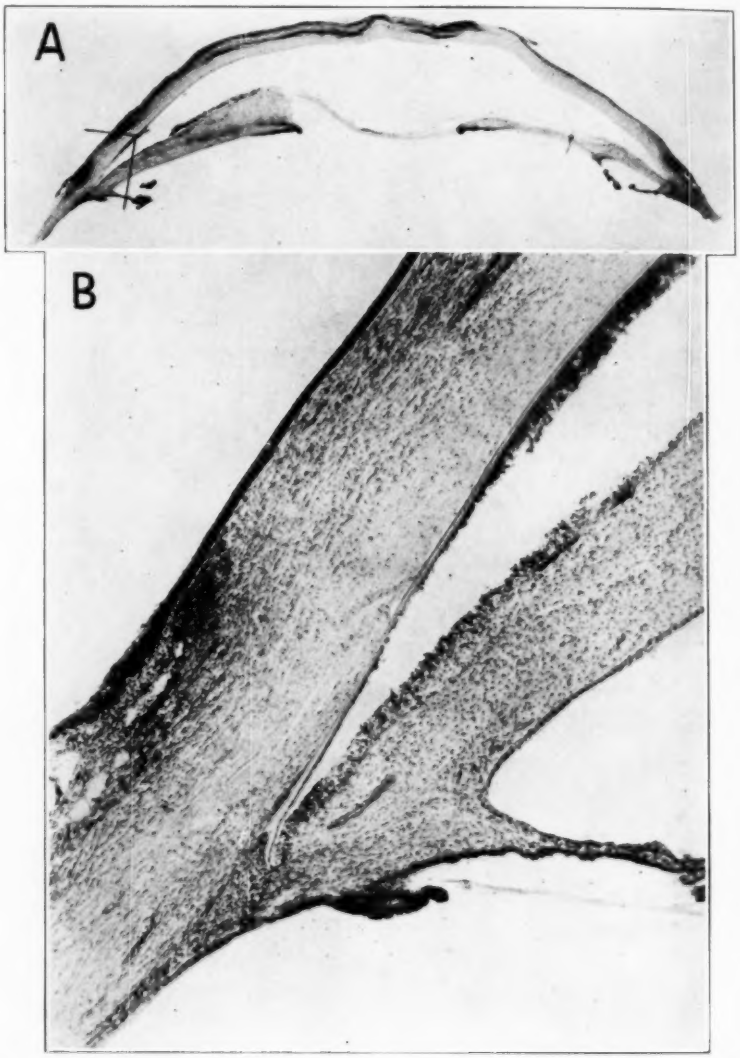

Fig. 5.—*A*, marked extension of the ulcer thirty-two hours after inoculation, showing continuity of the corneal infiltration from the ulcer to the limbus (× 6). *B*, high power view of the limbic region, showing a further advance of the corneal infiltration, more extensive infiltration of the iris and more marked exudation in the anterior chamber (× 55).

EFFECT OF ORAL ADMINISTRATION OF SULFAPYRIDINE SODIUM ON EXPERIMENTAL B. PYOCYANEUS INFECTION OF THE RABBIT'S CORNEA

COURSE OF INFECTION IN RABBITS TREATED PROPHYLACTICALLY

GROUP I.—*Treatment was instituted twenty-four hours before inoculation and subsequently continued for one to six days.*

The right cornea of 6 rabbits and both corneas of 18 rabbits were inoculated after the animals had been given two prophylactic doses of sulfapyridine sodium during the preceding twenty-four hours. A benign infiltration 1 to 2 mm. in diameter, accompanied by slight congestion of the ocular conjunctiva and the iris, appeared within six to eight hours. Three rabbits died during the course of treatment, which was continued for periods ranging from one to six days subsequent to inoculation. Of the surviving animals, 4 were treated for six days, 6 for two days, 6 for one and one-half days and 5 for one day. The ulcers showed little or no tendency to progress, the reactionary hyperemia remained almost uniformly mild, and in no instance did the aqueous become cloudy. All symptoms of congestion had subsided and the ulcers appeared healed in one to three days. Frequently a serious relapse occurred if treatment was discontinued after one day, but such relapses were largely avoided if treatment was maintained for a longer period. For this reason the rabbits are divided into two subgroups. In subgroup A are those treated for from one and one-half to six days, and in subgroup B are those treated only one day.

In all 5 eyes of the 3 rabbits in group I which died during the course of treatment, the inflammation was mild. No discharge appeared, cultures were negative and the ulcer healed without progression within one to two days after inoculation.

SUBGROUP A.—*Treatment continued for one and one-half to six days.*

Except in 1 instance, in which congestion increased slightly until the second day, the maximum inflammation was reached within a few hours in the 27 eyes in this group. As a rule the inflammation subsided rapidly and the ulcer healed without extension in from one to two days. However, in 4 eyes the ulcer progressed slightly, and healing was delayed until the third day. On the day following inoculation, B. pyocyaneus was recovered from all but 1 of the 4 eyes. In 2 eyes a relapse took place three days after treatment was discontinued. These were the eyes of a rabbit treated for one and one-half days, and the ulcer in each appeared to be healed twenty-four hours after inoculation. Both eyes became mildly congested, and the ulcers progressed moderately before healing, which occurred on the seventh and the ninth day, respectively. Repeated cultures failed to reveal B. pyocyaneus.

In this subgroup, in only 2 instances did the resultant scar exceed 4 sq. mm., whereas in the majority of instances the diameter of the scar was less than 1 mm. One rabbit died thre days after treatment was discontinued.

Control Eyes: In all 15 control eyes of this subgroup the infection was severe and virtually the entire cornea became involved. The lids were often swollen to the point of ectropion, the discharge was generally abundant and B. pyocyaneus was consistently recovered. A hypopyon, which usually became large, appeared in all eyes but 1, and the cornea ruptured in 12. The duration of the inflammation ranged from nine to fourteen days.

Figure 6 shows a comparison, in percentages, of the course and the outcome in the treated and the control group.

Subgroup B.—*Treatment continued for one day.*

In the 10 eyes in this subgroup the congestion was uniformly mild. There was no discharge, cultures were negative and the maximum inflammation was reached in less than twelve hours. In 8 eyes the inflammation subsided rapidly and the ulcers appeared to be healed twenty-four hours after inoculation; in 2 eyes the decline was more gradual and healing did not take place until the second day. In no instance did the resultant scar exceed 1 mm. in diameter. Three eyes remained unchanged, but in 7 a relapse occurred on the third day. In 2 eyes the relapse consisted merely of mild ocular congestion without apparent change in the corneal lesion. Cultures were negative, and on the following day the eyes were normal. However, in 5 eyes the inflammation was severe, a

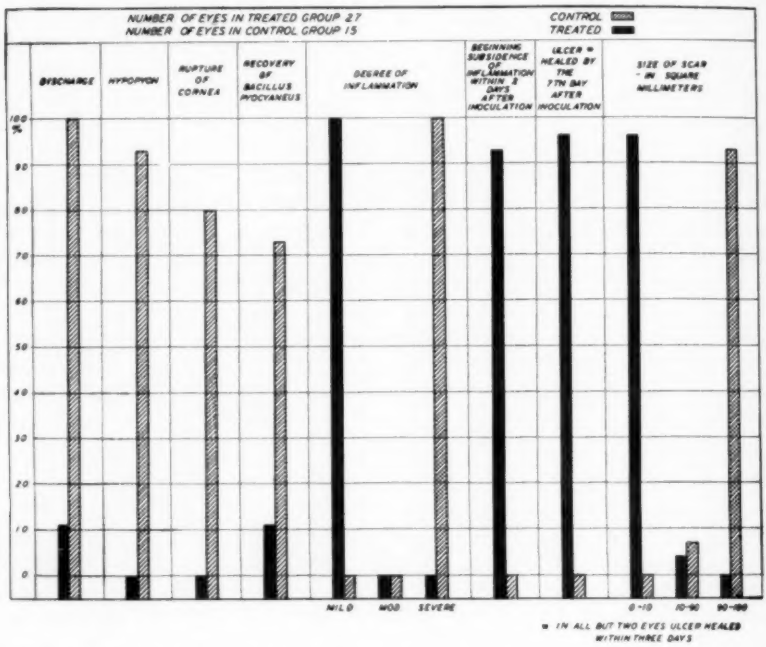

Fig. 6.—The results of prophylactic treatment instituted twenty-four hours before inoculation and subsequently continued for one and one-half to six days: a comparison, in percentages, of the course and the outcome in treated and control groups.

hypopyon developed and the ulcer became actively progressive. A discharge appeared on the swollen lid margins, and B. pyocyaneus was recovered. The ulcers healed in from seven to fourteen days, the resultant scar including about one third of the corneal circumference in 3 eyes and the entire cornea in 2. The rabbit in which both corneas were completely involved died three days after treatment was discontinued.

Control Eyes: In the 4 control eyes of this subgroup the infection was severe, and in 3 it appeared in the form of a ring abscess. The discharge was generally abundant, and B. pyocyaneus was consistently recovered. A hypopyon, usually large, appeared in all 4 eyes, and the cornea ruptured in 3. The duration of

inflammation ranged from fifteen to twenty-one days, and in every instance the resultant scar included the whole corneal circumference.

Because of the small number of eyes in this subgroup, a comparison in percentages of treated and control eyes is not justified.

GROUP II.—*Treatment instituted concurrently with inoculation and continued for two days.*

In 4 rabbits both corneas were inoculated concurrently with the beginning of treatment, which was continued for two days. The infection was mild, no discharge appeared, the cultures were negative, and the ulcer healed without extension in from one to two days. Two of the rabbits died two days after treatment was discontinued.

Control Eyes: In 1 of the 2 control eyes the infection appeared in the form of a severe ring abscess with hypopyon, resulting in the destruction of the entire cornea after early rupture. In the other eye a moderately severe progressive ulcer involved only about one fourth of the corneal circumference.

Comment on Prophylactic Series.—The foregoing experiments indicate that infection of the cornea with B. pyocyaneus is not prevented in rabbits that have received two prophylactic doses of sulfapyridine sodium orally during the preceding twenty-four hours. However, the drug does affect its course materially, and if the treatment is continued for twenty-four hours the inflammation subsides rapidly and the ulcer appears to be healed, with little or no extension, in from one to three days. Although all cultures of material taken after the second day were negative, viable organisms may apparently still be present if the treatment is not continued for a longer period. This is attested by the fact that in 70 per cent of the eyes a relapse occurred when treatment was suspended after twenty-four hours, whereas a relapse occurred in only 7 per cent when the treatment was continued for a longer time.

Not enough evidence has been presented to indicate equal effectiveness of treatment instituted concurrently with inoculation. However, such effectiveness is more than merely suggested, in spite of the fact that in 1 of the control eyes the infection was not severe. An attempt to repeat these experiments was unsatisfactory, as the virulence of the organism was low. Inoculation produced only a moderately severe infection in the control eyes, and the production of pyocyanin was poor. In the 12 eyes of 6 rabbits the ulcer healed without extension within twenty-four hours.

COURSE OF INFECTION IN RABBITS IN WHICH TREATMENT WAS INSTITUTED AFTER THE DEVELOPMENT OF ULCER

In two groups of rabbits treatment was instituted after the appearance of the ulcer and was continued for six days. In one group treatment was begun six hours after inoculation, and in the other group it was instituted twelve hours later.

GROUP I.—*Treatment instituted six hours after inoculation.*

Treatment was begun six hours after inoculation of both corneas of 24 rabbits.[69] At this stage the lesion usually appeared as a grayish, sharply circumscribed infiltration 1 to 2 mm. in diameter, accompanied by mild congestion of the conjunctiva and the iris. One animal died a few hours after inoculation.

In the 46 eyes of the surviving rabbits the course was generally mild and the outcome favorable. This was particularly true in 40 eyes, in which the ulcer had healed with virtually no extension by the time treatment was discontinued. In the 6 eyes in which infection persisted for a longer period the outcome was usually less favorable. In 1 eye a somewhat indolent ulcer did not progress after the sixth day. In another a moderately progressive ulcer with hypopyon gained momentum after medication was discontinued. In 4 eyes which had apparently responded well to therapy the subsequent course was particularly significant. At the time treatment was discontinued the inflammation, which had been mild, had nearly subsided and the ulcer was confined to the site of inoculation. One to three days later a relapse occurred. Although in 1 eye it was only moderately severe and there was no extension of the corneal lesion, in 3 eyes a hypopyon appeared and the ulcer progressed rapidly. Cultures, which had been consistently negative for B. pyocyaneus were positive on the seventh and the eighth day, respectively, for 2 of the eyes.

In this group the ocular congestion generally reached its height soon after inoculation and then subsided rapidly. The maximum inflammation was reached within less than twenty-four hours in 34 eyes, by the second day in 2 eyes and by the third or fourth day in 4 eyes. In 4 of the 5 eyes in which the inflammation was most severe between the seventh and the twelfth day, the severity represented a relapse which occurred after treatment was discontinued. The inflammation was mild in 41 eyes, moderately severe in 2 and severe in 3. In the 3 eyes in which it was severe and 1 in which it was moderately severe, the congestion had been mild during the course of the treatment. The lids were rarely affected, except for hyperemia of the margins and mild congestion of the palpebral conjunctiva. A slight discharge was present in 7 eyes. B. pyocyaneus was recovered from only 2 eyes, and in both instances the culture was positive during a relapse after treatment had been discontinued. A hypopyon appeared in 2 eyes during the course of treatment and in 3 eyes which suffered a relapse. The inflammation lasted from one to seventeen days, and in 40 eyes it had subsided by the end of the sixth day. In 24 of these eyes the ulcer appeared to be healed twenty-four hours after inoculation, whereas it was apparently healed in 3 by the second day and in 9 by the third or fourth day. In 6 eyes in which the inflammation persisted for more than six days it appeared about to subside when the treatment was discontinued.

As a rule the ulcer showed little tendency to progress, and in no instances in this group did the cornea rupture. In 41 eyes the resultant scar did not exceed 4 sq. mm. in area. In 3 eyes it ranged from 10 to 90 sq. mm., whereas in 2 the entire cornea was involved. One rabbit died two days after the treatment was discontinued.

Control Eyes: In 18 control eyes the infection was severe, and in 3 eyes it was moderately severe. As a rule the lids were swollen, discharge was abundant and cultures for B. pyocyaneus were consistently positive during the early days of infection. A hypopyon, which frequently attained considerable

69. An additional rabbit was rejected before treatment was begun because of the unsuccessful inoculation of both corneas.

size, appeared in 15 eyes, and in 9 eyes the cornea ruptured. The duration of inflammation ranged from ten to sixteen days, extending in 85 per cent for more than twelve days. The resultant scarring was generally extensive, virtually the entire cornea being involved in 16 eyes. In all but 1 of 5 eyes in which the scar was less extensive it included at least one half of the corneal circumference.

In figure 7 are compared, in percentages, the course and the outcome in the treated and the control eyes of this group.

Response to treatment was apparent in all the eyes in this group. The inflammation began to subside as a rule soon after medication was begun and in 74 per cent within the first few hours. In 87 per cent the course

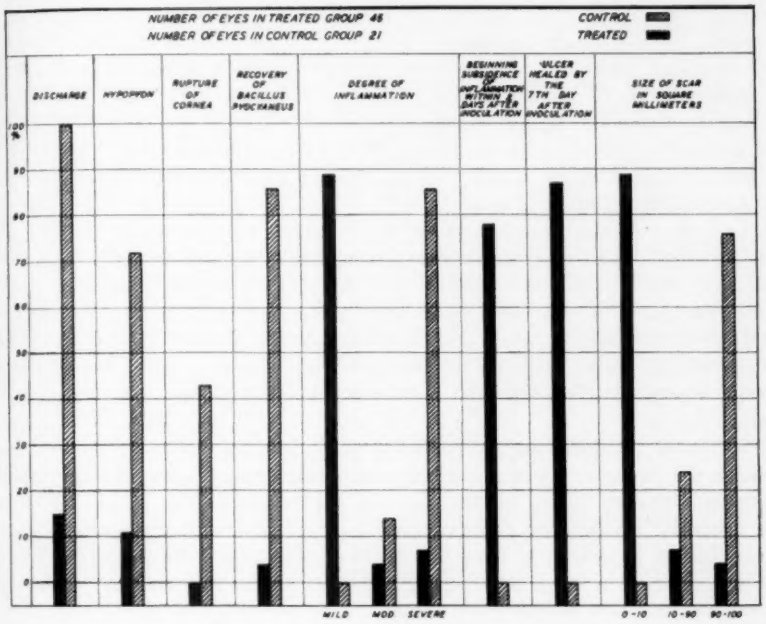

Fig. 7.—Results of treatment instituted six hours after inoculation and continued for six days: a comparison, in percentages, of the course and the outcome in treated and control groups.

was mild and the ulcer healed with virtually no extension by the sixth day. Treatment was particularly effective in 52 per cent, in which all signs of infection had disappeared twenty-four hours after inoculation. Although in 13 per cent of the eyes the course was prolonged and the outcome was generally less favorable, the treatment was apparently beneficial. An active infection was present when therapy was discontinued, but the progress of the ulcer appeared to be checked. In view of the subsequent course it is not unreasonable to assume that if treatment had been maintained over a longer period the outcome might have been more favorable.

A comparison of the control with the treated animals demonstrated that in every respect the course and the outcome were more favorable in the latter.

The results obtained in this group indicate that B. pyocyaneus infection of the cornea is favorably affected if oral treatment with sulfapyridine sodium is instituted within six hours after inoculation and is continued for six days.

GROUP II.—*Treatment instituted eighteen hours after inoculation.*

Treatment was instituted eighteen hours after inoculation of the right cornea of 27 rabbits and of both corneas of 35.[70] At this stage the infection had usually progressed considerably beyond that present six hours after inoculation. A grayish white ulcer 1 to 4 mm. in diameter, with ill defined margins, had developed. In many eyes the adjacent portion of the cornea was cloudy; frequently fresh areas of infiltration were present, and occasionally there was evidence of the beginning of an infiltration ring. There was moderate congestion of both the palpebral and the ocular conjunctiva, and often there was a barely perceptible amount of grayish white discharge. The iris was congested, but the anterior chamber remained clear. Eight animals died during the course of treatment, and 2 were discarded because of injury.

The course of the inflammation in the 82 eyes of the surviving rabbits was generally more severe and the outcome less favorable than in group I. However, in 47 eyes the inflammatory reaction was generally mild, all signs of infection having disappeared within twenty-four hours after the treatment was discontinued. Except in 1 instance, in which the lesion progressed moderately and the entire cornea became cloudy, the ulcer in these eyes healed with little or no extension. A small hypopyon, which appeared in 5 eyes, was usually transitory, disappearing within a day or two.

In 35 eyes the inflammation persisted for a longer period. In 19 of these, in which the outcome was generally favorable, the ocular congestion had almost completely subsided when medication was discontinued. The ulcer, which in most instances involved less than one fourth of the corneal circumference, healed without further extension in from one to five days. The inflammation had been more severe than in those eyes which had healed promptly, and in 8 instances a hypopyon had been present.

In 16 eyes in which inflammation persisted the entire cornea became involved. In 2 of these the congestion had been mild, and the ulcer appeared to be almost completely healed when treatment was discontinued. However, a serious relapse occurred on the following day, when a hypopyon appeared and both corneas were rapidly invaded. B. pyocyaneus was recovered from 1 eye on the eighth day. In 14 eyes the inflammation was severe almost from the outset. The ocular congestion was marked, and as a rule the lids were swollen and the discharge was abundant. A persistent hypopyon was present in all but 2 of the eyes, and the cornea ruptured in 7. In 6 of these eyes the progress of the ulcer was checked before treatment was discontinued, but the entire cornea was cloudy. In 8 the course was similar to that of the controls; the whole cornea was involved by the third or fourth day and in 5 it ruptured. In 5 of these eyes the infection appeared as a ring abscess and in 3 as a progressive ulcer. During the course

70. Two additional rabbits were rejected before treatment was begun because of unsuccessful inoculation.

of inflammation B. pyocyaneus was recovered several times from each of the 8 eyes.

In this group there was a tendency for the ocular congestion to increase during the first day or two in spite of treatment. However, the maximum inflammation was reached within the first two days in 45 of these eyes and within the first twenty-four hours in 21. In 31 eyes the inflammation increased until the third or fourth day, and in 6 it continued to increase until the fifth to the seventh day. The inflammation was mild in 41 eyes, moderately severe in 23 and severe in 18. In 14 eyes the lids were swollen, but never to the point of ectropion, and discharge was present in 46 eyes. Although B. pyocyaneus was recovered from 43 eyes, cultures were negative after the second or third day except in 11 instances. A hypopyon, usually small, appeared in 27 eyes, and the cornea ruptured in 7. The duration of inflammation ranged from one to sixteen days. Of the 47 eyes in which the inflammation subsided by the seventh day the ulcer appeared healed twenty-four hours after inoculation in 11, by the second day in 2 and by the third day in 1. The resultant scar did not exceed 10 sq. mm. in 45 eyes (in 33 of these the mean diameter was 2 mm. or less); in 20 eyes it ranged from 10 to 90 sq. mm.; whereas in 17 the entire cornea was involved.[71]

Figure 8 presents a fairly typical example of various stages of infection in an eye in this group in which the outcome was favorable.

Control Eyes: In 32 control eyes the infection was severe; in 8 it was somewhat milder. As a rule the lids were swollen, and the discharge was generally abundant. B. pyocyaneus was consistently recovered. A hypopyon, usually large, appeared in 32 eyes, and the cornea ruptured in 21. In 1 eye the inflammation subsided on the eighth day, but as a rule it persisted for ten to twenty-one days. In 32 eyes the resultant scar included virtually the entire cornea; in 3 it involved one third or more of its circumference, and in 5 it was comparatively small.

In figure 9 are compared, in percentages, the course and the outcome in the treated and the control eyes of this group.

Although in this group treatment was generally effective, the response was less marked than in group I. The ocular congestion was

71. It may be of some interest to report the course and the outcome in the rabbits whose treatment was discontinued because of injury or death. In 2 rabbits medication was suspended because of injury. In 1, whose therapy was discontinued after the first day, the eye was mildly congested, and the ulcer, which was 1 by 3 mm. in size, remained stationary for two days. It then became more active, and it progressed until about one half of the cornea was involved. Cultures were negative until the sixth day following inoculation. In another rabbit the ulcer had apparently healed when treatment was discontinued on the fourth day. The course had been extremely mild, and only a faint 1 mm. scar remained. Reactivation occurred two days later, the ulcer rapidly invading the whole corneal circumference. A hypopyon which reached 3 mm. in height appeared five days after treatment was discontinued. Cultures were negative until the tenth day after inoculation.

During the course of the treatment 8 rabbits died between the third and the sixth day. In 7 of 13 eyes the ulcer had apparently healed, with little or no extension. In 2 eyes the congestion was slight and the ulcer had not progressed in the preceding twenty-four hours. In 3 the ulcer was slowly progressive and was accompanied by moderate ocular congestion, a hypopyon appearing in 1. In 1 eye the infection was in the form of a ring abscess with hypopyon.

usually more pronounced, discharge occurred more frequently and in greater abundance, B. pyocyaneus was recovered in a higher percentage of instances, a hypopyon occurred more frequently and was inclined to be larger and there was a greater likelihood of corneal ruptures taking

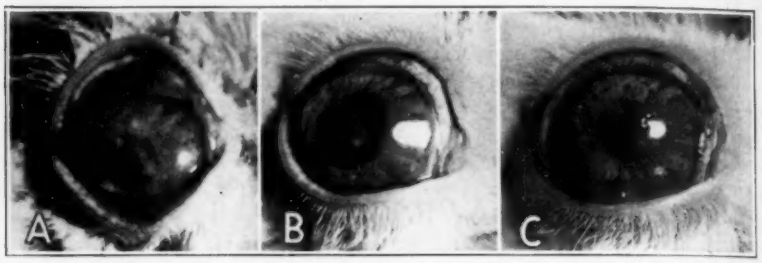

Fig. 8.—One eye of rabbit 37, whose treatment was instituted eighteen hours after inoculation, eighteen hours (*A*), forty-eight hours (*B*) and four days (*C*) after inoculation.

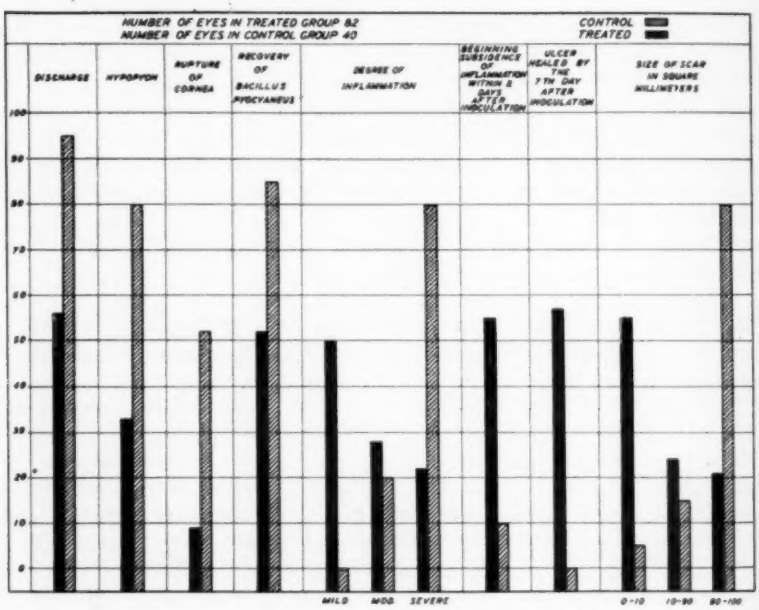

Fig. 9.—Results of treatment instituted eighteen hours after inoculation and continued for six days; a comparison, in percentages, of the course and the outcome in treated and control groups.

place. The inflammation showed a greater tendency to increase in severity during the early days of treatment, and it usually subsided less rapidly. In addition, the course was generally more prolonged and the outcome less favorable.

A definite response to treatment was apparent in 80 per cent of the eyes. In 26 per cent the inflammation began to subside shortly after the first dose was administered, and in 13 per cent the ulcer appeared to heal within twenty-four hours after inoculation. Altogether, 57 per cent of the ulcers were healed by the end of the seventh day, and 40 per cent healed with little or no extension. In 43 per cent of the eyes the inflammation persisted for a longer period. Of these, 23 per cent were definitely influenced by treatment. In spite of the frequent occurrence of somewhat extensive corneal involvement, the progress of the ulcers was checked before treatment was discontinued, and they healed without further extension. In 20 per cent of the eyes there was little or no response to treatment and the outcome was uniformly unfavorable. Of these, treatment was temporarily helpful in 2 per cent and of questionable value in 8 per cent but wholly ineffective in 10 per cent.

A comparison with the control eyes showed that in the treated rabbits of this group the inflammation was as a rule less pronounced, complications ensued less frequently, the course was shorter and the outcome was more favorable.

The results obtained in this group indicate that in general B. pyocyaneus infection of the cornea is affected favorably if oral treatment with sulfapyridine sodium is instituted eighteen hours after inoculation and is continued for six days; however, they indicate that treatment would be more effective if begun twelve hours earlier.

SUMMARY

The seriousness of B. pyocyaneus ulcer of the cornea warranted an investigation of possible therapeutic measures to combat it. No measures that are certain to be effective have been reported either experimentally or clinically. Local therapy has probably failed because of the rapid migration of the organisms from the site of infection to other parts of the cornea.

Chemotherapy offered a possible means of attack on the organisms within the corneal stroma. Sulfapyridine rapidly penetrates the cornea, does not as a rule have a deleterious effect on normal tissue and fluid elements and is bactericidal against certain organisms in concentrations that can easily be attained by therapeutic administration.

The in vitro experiments indicated that sulfapyridine sodium in 10 per cent concentration is bacteriostatic against three of the four strains of B. pyocyaneus tested.

In vivo, the oral administration of sulfapyridine sodium proved of definite value. Given prophylactically, the drug did not prevent infection of the cornea, but it materially affected the course of the disease; the

ulcer healed, with virtually no progression, in from one to three days if treatment was continued for twenty-four hours. Relapses, which usually occurred when medication was discontinued at this time, could almost always be avoided if the treatment was maintained over a longer period.

A response to treatment was apparent in all animals receiving sulfapyridine sodium six hours after inoculation, and in 87 per cent the ulcer healed with little or no extension during the course of the treatment. In 13 per cent, in which inflammation persisted for a longer period, the progress of the ulcer appeared to be checked when treatment was discontinued, but the ulcer recurred in 11 per cent.

The response to therapy was less marked when medication was instituted eighteen hours after inoculation, but a favorable effect was apparent in 80 per cent of the eyes. In 57 per cent healing occurred during the course of the treatment, 40 per cent showing virtually no extension of the ulcer. The course of the inflammation was prolonged and the outcome generally unfavorable in 43 per cent of the eyes, 23 per cent being definitely influenced by treatment but 20 per cent showing little or no response.

The concentration of the drug in the blood proved extremely variable both in different rabbits and in the same rabbit on different days. In general no relation could be found between the concentration and the course and outcome.

In the control eyes the course was almost uniformly severe and the outcome unfavorable.

CONCLUSIONS

As a result of these studies it may be concluded that the oral administration of sulfapyridine sodium is effective in the prophylaxis and the treatment of experimental B. pyocyaneus ulcer of the rabbit's cornea and that the efficacy of the treatment varies directly with the promptness with which it is instituted. It may further be concluded that the degree of concentration of the drug in the blood shows no apparent relation to the course and the outcome of the infection.

In view of the similarity in clinical course of the ulcer in the rabbit eye to that in the human eye, it would seem that chemotherapy with sulfapyridine or other of the sulfanilamide compounds should be prescribed for the latter.

Miss Alice Westcott acted as technical assistant, and Miss Stella Zimmer took the photographs.

EYE WORM (THELAZIA CALIFORNIENSIS) INFECTION IN MAN

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M. A. STEWART, PH.D.

AND

EDWARD I. SUGARMAN, B.S.

SAN FRANCISCO

The purpose of this paper is to report the occurrence of infection in a human being with a nematode worm, Thelazia californiensis, and to call attention to the fact that helminthologists believe that such infection may occur in man more frequently than is indicated by the paucity of recorded cases.

While the symptoms produced by this worm are mild, the damage done to ocular tissues is negligible and a complete cure can be effected by removal of the parasites, the patient may exhibit great apprehension and mental distress.

Apparently the conjunctival sac is the normal habitat of this particular worm, but it should be borne in mind that parasitic worms frequently produce a more serious pathologic picture when they fail to gain the preferred organ or tissues and become erratic in their migratory behavior than when they attain their goal by orthodox paths of migration. Erraticism is more common than it was formerly believed to be, particularly in the case of Trichinella spiralis, the round worm which causes trichinosis; the common liver fluke, Fasciola hepatica; filarial worms; lung flukes, and the immature forms of the various species of tapeworms. For some unknown reason, erratic helminths rather frequently invade the eye and adjacent tissues.

The patient was a policeman 35 years of age in excellent health except for alopecia universalis. His eyes had been examined in December 1935, September 1937 and March 1940. On each occasion he complained of ocular fatigue, photophobia and inability to read for more than an hour or two.

There was a complete absence of eyebrows and eyelashes, the skin was unusually blond but not albinotic and the irises were very light blue. The pupillary reactions were normal, the media clear and the fundi normal. The patient was practically emmetropic, his extraocular muscle balance was perfect and his accommodation and convergence adequate; the fields of vision and the intraocular tension were normal, and the nasolacrimal ducts were patent. An unusually comprehensive examination was necessary on each occasion in order to reassure him. No glasses or other therapeutic measures were prescribed.

On July 11, 1940, in addition to his usual complaints he stated that he had "the sensation of something in the left eye that moved about." In spite of the absence of cilia, the lids were easy to turn. The eye was examined with oblique illumination and a Berger loupe. At first nothing abnormal was seen, but just as the slit lamp and corneal microscope were being prepared for use, what appeared to be a raveling from a bit of gauze (except that the ends seemed cut off too abruptly) flashed into view on the upper temporal quadrant of the bulbar conjunctiva as the patient rolled his eyes about under the strong light. The object moved slightly and assumed a U-shaped contour, while when first seen it had been almost straight. It was easily removed on an applicator, on which it moved slowly about until it was placed in solution of formaldehyde. Careful search over every square millimeter of the conjunctival sacs of each eye failed to reveal any more worms, ova or other adventitious material.

The patient was not seen again for five days. Five more worms were then removed from the conjunctival sac of the same eye. Thereafter he was examined daily for a week, but no more parasites were found. He was next examined seven months later (May 1, 1941), but nothing abnormal was observed.

After the first worm was found an examination of the blood revealed no abnormalities. There was no eosinophilia. He had not been in close contact with any dogs or other animals, but he had been on a vacation in the Sierra Nevada mountains during the previous month. He did not remember having been bitten by any insects.

He had had numerous physical and laboratory examinations by several competent physicians in San Francisco and in May 1940 had gone to the Mayo Clinic in the hope of finding a cure for his alopecia. At that time he was mainly concerned about his alopecia and did not stress his ocular symptoms. It was noted that his visual acuity was normal; the external examination and examination of the fundi gave normal results, and no parasites were seen. As a matter of interest several of the parasites were sent to Dr. William L. Benedict and were identified by Dr. T. B. Magath, Section of Clinical Laboratories, Mayo Clinic, as T. californiensis.

In the meantime the parasites had been identified in Berkeley, Calif., by Prof. Charles A. Kofoid, and they were later identified and studied by one of us (M. A. S.).

The only case of T. californiensis infection in man previously reported occurred in Porterville, Calif., in 1928.[1] Dr. Austin Miller removed three of these nematode worms, which were identified, studied and reported on by Prof. Charles A. Kofoid, from the right eye of a Dr. G., a practicing physician, at that time 42 years of age, who had been a resident of California for six years. The only thing in the previous history which Dr. Miller considered worthy of mention was that the patient had gotten a gnat or some other flying insect in the eye ten days before while on a trip in the Sierra Nevada mountains.

Whereas the case reported in this paper is the second recorded instance of infection with T. californiensis in man, 4 other cases of infec-

1. Kofoid, C. A., and Williams, O. L.: The Nematode Thelazia Californiensis as a Parasite of the Eye of Man in California, Arch. Ophth. **13**:176-180 (Feb.) 1935.

tion with a closely related parasite, Thelazia callipaeda, have been reported from China.

The parasites in the present case were all females 10 to 12 mm. long and 0.5 mm. in diameter. When viewed with a loupe they appeared uniform in diameter; the slightly tapered anterior and posterior extremities were not strikingly apparent. With the sclera as a background the worms appeared a translucent grayish white, but against a white cotton background they were more distinctly grayish and the transverse cuticular striations were visible. Higher magnification was necessary to reveal the anatomic details in the fresh specimen. The males are about one third smaller than the females and possess a characteristic conspicuously recurved posterior extremity. This species was first described by Price [2] in 1931. The measurements given by Kofoid and Williams [1] for the specimens in the case previously reported are all somewhat smaller than for the specimens secured from sheep and deer. The specimens in the present case were about the same size as those reported by Kofoid and Williams.[1] The measurements of specimens from dogs, which were later described by Kofoid, Williams and Veale,[3] are intermediate in size.

We believe that this difference in size indicates that the infection in man and the dog is accidental and that the natural hosts are herbivorous animals,[4] since it is well known that resistance on the part of the host to a number of nematode parasites is manifested by a dwarfing of the worm. Further evidence as to the preference of T. californiensis is shown by the fact that careful search in the eyes of sheep dogs which were constantly in contact with heavily infected flocks of sheep failed to reveal T. californiensis.

T. californiensis must be differentiated from twenty other members of the genus Thelazia. All these species deposit fully embryonated eggs and live in the lacrimal duct, conjunctival sac, eye or nictitating membrane of mammals and birds. The infection is usually bilateral in natural hosts, but in all the cases of infection in man it was unilateral.

The 4 cases of thelaziasis in man that were reported from China were all identified by competent authorities as instances of infection with T. callipaeda, the "Oriental eye worm," first described in 1910 by Railliet and Henry.[5]

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2. Price, E. W.: A New Nematode Parasitic in the Eyes of Dogs in the United States, North Am. Vet. **12**:49-58, 1931.

3. Kofoid, C. A.; Williams, O. L., and Veale, N. C.: Thelazia Californiensis, a Nematode Eye Worm of Dog and Man, with a Review of the Thelazias of Domestic Animals, Univ. California Publ., Zoöl. **41**:225-234, 1937.

4. Stewart, M. A.: Ovine Thelaziasis, J. Am. Vet. M. A. **96**:486-490, 1940.

5. Railliet, A., and Henry, A.: Nouvelles observations sur les thélazies, nématodes parasites de l'oeil, Compt. rend. Soc. de biol. **68**:783-785, 1910.

Whereas little is known of the symptomatology of infection in man with T. californiensis, a certain amount of information has been collected relative to the symptomatology of infection with T. callipaeda. Worms of this species ordinarily produce little conjunctivitis but markedly stimulate the secretion of lacrimal fluid. The cornea may gradually become opaque. Intense pain and extreme nervous symptoms have been reported.

Faust,[6] in his excellent book, recommended cocainization of the eye before removal of the worms. We believe that the use of cocaine for this purpose in human beings is not only unnecessary but dangerous. If the parasite is on the cornea it can easily be washed off with a few drops of physiologic solution of sodium chloride and picked up from the conjunctiva with an applicator. Tweezers are unnecessary. It would seem that cocaine solution would tend to be absorbed by the parasites and render them less motile and hence less easily seen, although this point was not verified.

It is agreed that the only damage the worms do in man or in animals is to produce discomfort, excessive lacrimal secretion and in some cases scarification of the cornea with subsequent ulceration. It is difficult to be certain that all the worms have been removed at a single examination. If the cornea is anesthetized, parasites which may have been overlooked can abrade the epithelium without the patient's knowledge.

T. californiensis should not be confused with two somewhat similar parasitic worms. The first of these is Onchocerca volvulus, which is fairly common in parts of southern Mexico and Central America as well as in Africa. This helminth is from two to five times the length of T. californiensis and is transmitted by the bite of any one of several species of black flies (which belong to the genus Simulium), which serve as necessary intermediate hosts. The larvae are sucked from the tissues of the infected person when the insect feeds, undergo a metamorphosis in the intermediate host and ultimately attain the infective stage. The infection is passed on to another susceptible person during a subsequent feeding.

The infective larvae apparently make their way through the tissues, as they are never found in the circulating blood. The site of the bite bears no relation to where the lesions may appear. A nonsuppurating, firm, fibrous tumor mass of variable size develops as an insulation around the worms even before they are sexually mature and is usually fully formed in less than a year after infection. In the new world the tumor masses are found most frequently on the scalp, whereas in Africa they are more commonly found on the elbows, knees, trochanters and ribs.

6. Faust, E. C.: Human Helminthology, ed. 2, Philadelphia, Lea & Febiger, 1939.

Each nodule contains at least one male and one female adult worm and swarms of larvae which tend to migrate to the region of the eyes. They may invade the cornea and provoke a punctate, vascular or interstitial keratitis. They may wander into the eyeball and produce congestion and hemorrhage around the limbus and edema and congestion of the conjunctiva. This stage is frequently followed by inflammation of the iris, ciliary body, retina and choroid and exudate into the vitreous, or the worms may invade the optic nerve and quickly produce blindness. No satisfactory treatment for Onchocerca volvulus has been devised. Excision of the subcutaneous nodules wherever found is helpful in reducing the number of larvae which may migrate to the ocular regions.

The other parasite from which T. californiensis must be differentiated is Loa loa, sometimes known as Filaria loa, the eye worm native in Africa. This parasite was introduced into the new world on numerous occasions in African slaves during the latter part of the eighteenth century. Also, infections with it have been reported from time to time in the United States in the eyes of persons who have resided in Africa and acquired it there. The parasite has not established itself in the new world, presumably because, so far as is known, the required intermediate hosts, which are flies belonging to the horse fly and deer fly family (Tabanidae), are confined to Africa.

Adults of the species L. loa are from three to seven times the length of T. californiensis and about the same diameter, but they lack the transverse striations. The life cycle is similar to that of Onchocerca except that the larvae are found in the circulatory blood as well as in the tissues under the skin. The adult worms live in the subcutaneous tissue, where they migrate back and forth and may not cause symptoms but often produce transient swellings, which are known as calabar, or fugitive, swellings. They have been found in all parts of the body but have a predilection for the head and, unlike Thelazia, are found beneath the conjunctiva or skin or deep in the tissues.

Nothing is known of the life cycle of T. californiensis, and the mode of infection is a matter for speculation. It is presumed that the parasite probably requires an arthropod intermediate host because parasitic worms, including the eye worm of chickens (Oxyspirura mansoni), which habitually invade the eyes of man and the lower animals are known to require insects as intermediate hosts.

T. californiensis thus far has been reported only from California, but its distribution in animals in that state is so widespread that one is justified in believing that it may be found throughout the Western states.

All investigations to date indicate that infection with this parasite, both in man and in lower animals, is acquired in hilly or mountainous

areas which are more or less covered with brush. Sheep, deer, black bears and dogs are known to have been infected with this species.

Douglas [7] stated that most of the infected dogs he studied were seen in the winter and spring. In view of the instances of infection observed in human beings, sheep and deer, we are inclined to believe that the infection is usually, if not always, acquired during the summer and fall. Douglas' belief may possibly be due to the fact that the dogs in question had been infected for a considerable period before a diagnosis was made. We believe, from a study of the infection in a human being and from observations on sheep, that the interval between infection and the appearance of the worms in the eye is short—probably three to four weeks.

SUMMARY

The second case of infection with T. californiensis in man is reported.

Infection with this parasite is presumably rather benign, but trauma of some magnitude may occur.

The history in the present case substantiates the opinion that infection is acquired in hilly or mountainous country that is covered with brush during the summer months.

Cocainization of the eye should be avoided in removal of the parasites.

The chief distinguishing features between T. californiensis and other nematodes that commonly invade the eye are pointed out.

450 Sutter Building.

7. Douglas, J. R.: A Survey of Canine Thelaziasis in California, J. Am. Vet. M. A. **93**:382-384, 1938.

OXYCEPHALY

TWENTY-FIVE YEAR REPORT OF A CASE FROM AN OPHTHALMOLOGIC VIEWPOINT

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Oxycephaly is a congenital abnormality of the bones of the skull in which the shape is that of a high dome or tower. It is often called steeple head, or *Turmschadel*. It is due to premature synostosis of the bones of the skull. Oxycephaly, or synostosis cranii, may further be classified as (1) scaphocephaly, narrow head with elongation from before backward, with a bulging forehead and occiput; (2) dolichocephaly, a long narrow skull, and (3) brachycephaly, a short wide skull.

Fowler,[1] referring to Rubin's[2] survey of oxycephaly, listed the commoner ocular changes as optic nerve atrophy, amaurosis, exophthalmos, divergent strabismus and nystagmus. Wechsler[3] stated that narrowing of the optic foramen is also present. In the case of oxycephaly I shall report on there were amaurosis, divergent strabismus, unequal exophthalmos and bilateral optic nerve myelination.

In a large percentage of oxycephalic persons the ocular defects listed were found. Holt[4] stated that the resulting impairment of vision varies in severity from slight interference with sight to complete blindness and that cerebral decompression may retard the optic changes. In the case I shall report three temporal decompressions were done.

Oxycephaly may be associated with hydrocephalus, and the mentality may or may not be normal. It may be confused with hypertelorism, described by Berliner and Gartner[5] as a congenital anomaly of the skull

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1. Fowler, J. G.: Spontaneous Luxation of the Eyeball: Report of an Instance in a Brachycephalic Patient, J. A. M. A. **116**:1208 (March 28) 1941.

2. Rubin, M. I.: Premature Synostosis and Associated Phenomena, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1940, vol. 4, chap. 25.

3. Wechsler, I. S.: A Text Book of Clinical Neurology, ed. 2, Philadelphia, W. B. Saunders Company, 1932, p. 512.

4. Holt, E. L.: Diseases of Infancy and Childhood, ed. 7, New York, D. Appleton and Company, 1920, p. 778.

5. Berliner, M. L., and Gartner, S.: Hypertelorism, Arch. Ophth. **24**:691 (Oct.) 1940.

and face characterized by a wide separation of the orbits and causing the eyes to be far apart.

Because the following case has been observed for over twenty-five years and because it is being reported from an ophthalmologic viewpoint, I thought that it would be of interest.

REPORT OF CASE

E. M., a white girl aged 9, was sent to the neurologic clinic at the Peter Bent Brigham Hospital, in Boston, on May 27, 1916 for complaints of headache, vomiting, nervousness, squint and failing vision. Her referring physician stated that she had marked exophthalmos and that the right eye could see at 15 feet 457 cm.) and the left eye was blind. (The sizes of the test objects were not given.)

On June 7 a neurologic examination by Dr. Horrax revealed that the head was unusual in appearance, being of oxycephalic configuration with a tendency to elevation over the parietofrontal region. There was decided bilateral exophthalmos, the left eyeball possibly protruding more than the right. The pupils were unequal; both reacted to light, direct and consensual, and in accommodation. Divergent strabismus was marked. The movements of the eyeballs were normal in all directions except when the patient looked down with the right eye. There was fine nystagmus when she looked to the right. There was ptosis of the lids. The reading vision was good, the patient being able to read ordinary print at a normal distance. No hemianopia was apparent on rough testing. Fundus examination of the right eye showed the disk to be a little pale, with the margins slightly blurred. The optic cup and the lamina cribosa were not visible. There was considerable new tissue formation. The vessels were somewhat tortuous. Extending from the upper edge of the disk, there was a whitish area about the size and shape of half an optic disk. It faded off irregularly into the periphery and was streaked irregularly with brownish pigment. Otherwise the periphery was clear. Except for the whitish area, the appearance of the left eye was similar, the picture being that of secondary optic nerve atrophy with the lamina and the optic cup obscured by new tissue. The periphery was clear.

On July 3 a right subtemporal decompression was done by Dr. Harvey Cushing. The operative note stated that a moderate amount of subdural fluid was secured, its removal helping to lower the intracranial pressure.

On July 15 the patient was reexamined by Dr. Horrax, who noted that there had been no change in her condition. She felt well and was up and about. There was no headache. Bilateral exophthalmos was still present. The inferior rectus muscle of the right eye remained practically paralyzed, so that the eye looked upward. The appearance of the fundi was the same as before.

On Aug. 23, 1919 the patient returned for observation. The inferior rectus muscle was still paralytic. The decompression area was not bulging. The general development was normal.

On May 21, 1921 the patient reported that there had been no headaches. The exophthalmos was much less. There was no nystagmus.

On May 23 a roentgenologic report by Dr. Harvey Cushing revealed that the skull in the right lateral position was seen to be somewhat peculiarly shaped,

with no evidence of suture lines. There were an erosion of the tables of the skull in the temporoparietal region and some convolutional atrophy of the inner table.

Twelve years later, on Sept. 1, 1928, the patient again was examined. She had had no headaches for many months. The vision was much better than before decompresison. She read small newspaper print without difficulty. However, she was aware that the vision in the right eye was poor. The exophthalmos was about the same as at the last examination, greater in the right eye. There was still palsy of the right inferior rectus muscle. The disks showed slight pallor and slight secondary atrophy, with adjacent white areas due to retinal anomalies. The visual acuity was normal in the left eye and about 20/200 in the right. The skull was without sutures; the pressure was increased, but there was no cranial deformity.

Twenty years later, on Nov. 12, 1936, the follow-up record stated: "This is a remarkable case. The patient, aged 29, was first seen at this hospital twenty years ago, at which time she was operated on by Dr. Cushing for synostosis cranii. She was having marked visual difficulties and severe headaches, and her mental development seemed poor. After a decompresison on the right she has done well. She has been through the sixth grade, apparently with fairly good marks, and was doing useful work until a few months ago. During the last few months she has had a recurrence of the headaches, marked dizziness and an attack of petit mal. She was referred here for further therapy. Examination shows slight bilateral exophthalmos, paralysis of the left inferior rectus muscle and paleness and blurring of the optic disks without choking. The reflexes are normal. The patient was seen by Dr. Cutler, who believes further operative procedures are indicated. Signs of increased pressure are present, and the old decompression area is almost entirely covered with bone, so that it no longer acts as a decompressor."

Because of financial conditions the patient left the Peter Bent Brigham Hospital clinic and went to the Massachusetts General Hospital. Her complaints were now headaches and attacks of dizziness, which compelled her to stop work. The results of physical examination were similar to those of Nov. 12, 1936 except that slightly greater exophthalmos of the right eye and a greater widening of the right palpebral fissure were revealed. The disks showed secondary atrophy.

On Dec. 8, 1936 the right temporal decompression area was enlarged, with subsequent relief of the symptoms. The operative note stated that the twenty year old decompression area had entirely recalcified in the peripheral two thirds.

The patient got along well for the next nine months, after which she began to complain of headache on the top of her head and in the left parietal region.

On Sept. 16, 1937 she was reexamined at the Massachusetts Eye and Ear Infirmary. The ophthalmologic examination showed moderate exophthalmos in both eyes with hypertropia in the right. The depressor muscles were paretic. The pupils reacted well. There was no papilledema of the disks, and physiologic excavation was absent. The retinal vessels were not engorged. Many medulated fibers were present in each eye. The exophthalmometer registered 20 mm. for the right eye and 18.5 for the left. The vision was about 1/200 in the right eye and 20/20-4 in the left.

A left subtemporal decompression was done on Oct. 14, 1937. Complete relief of the headaches and dizziness was obtained.

Twenty-four years later, on April 30, 1940, I examined the patient in my office. She was now 33 years of age. Her right eye was amblyopic and her vision in that eye the perception of fingers at 6 feet (183 cm.). The vision of her left eye was 20/20 with and without glasses. There was slight exophthalmos in each eye. Her consensual reflex was normal. The optic disk of the right eye was pale pink. Almost completely surrounding the disk there was a white irregularly projecting area extending peripherally about ½ to 1 disk diameter. The retinal vessels were almost completely obscured but were clearly seen immediately after leaving this area. The peripheral part of the fundus appeared normal, as did the cilioretinal vessels. The left disk also had an area of white retinal tissue

Fig. 1.—The patient Oct. 12, 1941.

around it, but this was not as extensive as in the right eye. No cupping of the disk was seen. The retinal vessels were similar to those of the right eye. The right eye continued to be in a hyperexotropic position.

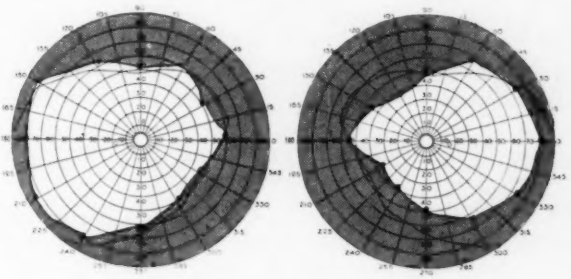
On Oct. 11, 1941, twenty-five years after her first operation by Dr. Cushing, I again examined the patient. She stated that she felt fine and that she had had no headache or dizziness since her last operation, in 1937. She was working in a cloth-weaving mill. She had eighteen brothers and sisters, of whom ten were living. No other member of the family had a similar condition of the skull. The patient impressed me as being of average intelligence.

Examination of her eyes showed vision to be perception of fingers at 4 feet (122 cm.) in the right and 20/20—3 in the left. There was no nystagmus. When looking into distance the right eye assumed a hyperexotropic position (fig. 1). This eye could not be rotated in the down and in and the down and out

position, a fact indicating paresis of the right inferior rectus and the right superior oblique muscle. The fact that the eye at rest assumed a hyperexotropic position would also indicate a secondary contracture of their antagonist muscles. The right eye diverged approximately 35 degrees by perimetric measurement. Both pupils accommodated to light and convergence. The punctum proximum of the left eye was 9 inches (23 cm.), leaving an amplitude of accommodation of about 4.5 D.

The fundi were essentially the same as I found on my examination eighteen months before.

A chart of the peripheral visual field of the left eye, taken with a white 3 mm. target, showed no contraction or depression (fig. 2 *A*). The central field of this eye, charted with a 3 mm. object at 1 meter, showed enlargement of the blindspot peripherally about 4 degrees. The peripheral field of the right eye showed a concentric contraction and depression for a 3 mm. target at 300 mm. (fig. 2 *B*). It was difficult to chart any definite field at 1 meter for this eye.



2 A 2 B

Fig. 2.—*A*, the peripheral visual field of the left eye, charted with a 3 mm. test object at 300 mm. *B*, the peripheral visual field of the right eye, taken with a 3 mm. test object at 300 mm., showing concentric contraction.

COMMENT

While optic nerve atrophy has been commonly found in oxycephalic patients by other observers,[2] I could find no evidence of it at my examinations. Its absence was borne out by the absence of any defect in the patient's left visual field, her normal fields for colored test objects and her normal vision. The right visual field, I believe, was explainable by the amblyopia. The myelination of the optic fibers of both eyes is a congenital anomaly of no pathologic significance.

In view of the temporal decompressions, there must have been factors other than pressure to explain the persistence of exophthalmos. The patient was first admitted with marked exophthalmos, and twenty-five years later she still had slight exophthalmos. These are relative terms, and the questions arise: Did the decompressions influence the exophthalmos? Why did the exophthalmos not entirely recede? Is the answer solely on a congenital basis?

A further question arises as to what caused the amblyopia and the ocular divergence. These were noticed at her first examination in 1916. Did the amblyopia cause the divergence or did the divergence cause the amblyopia—an ever present question in all such cases—? Did the increased intracranial pressure, for which she was operated on, affect the right optic nerve, which in turn caused amblyopia and then divergence? If so, then relief of her ocular symptoms specifically by cerebral decompressions did not help her, since twenty-five years later she was still amblyopic in one eye—as she originally was. Curiously enough, she was first reported blind in the left eye, with vision at 15 feet in the right. At her subsequent examinations, including the most recent, it was her left eye which saw well and her right which was amblyopic. I am at a loss to explain this aspect of the case. Possibly more study of this type of case may lead to a solution of this and other problems.

SUMMARY

The ocular aspects of a case of oxycephaly are described. Treatment consisting of three cerebral decompressions over a period of years and its effect on the ocular apparatus twenty-five years later are discussed.

Solely from an ocular viewpoint, doubt has been raised as to the beneficial effects on the ocular system of temporal decompression in a case of oxycephaly.

DIAGNOSTIC AIDS IN THE STUDY OF GLAUCOMA

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BROOKLYN

I. GRAPHIC RECORD

To ophthalmologists who have tried to make a detailed study of data collected from a series of cases of glaucoma, it has seemed desirable to use some method of graphic representation. Even if one is not particularly interested in analyzing a large number of cases, it is a great advantage to be able to review the progress in a particular case by a glance at a chart. The alternative is to review all the data from often voluminous records at a time when one is occupied with busy office routine. The following paragraphs present an outline showing the purpose and the use of a graph form which after much modification has been found practical and useful in the office, the glaucoma clinic and the ward.

One would think that there would be no great complication in devising a useful graph form for the visualizing of a series of tonometric readings, but a simple plotting of variations in pressure has little significance in the absence of related data. To make this statement clear, it is only necessary to point out that such secondary data as the facts concerning ocular medication, catharsis, time of day and visual acuity must be considered in the interpretation of even a single tonometric reading.

Patients with glaucoma are studied under various conditions, each of which demands an appropriate routine.

On the one hand, a patient suffering from an acute or subacute attack of glaucoma may require three to six visits a week, or, on the other hand, he may need repeated examination during a single visit. If he is sent to a hospital, it may be necessary to make certain studies hourly or even more often.

Perhaps the patients needing the most diverse form of investigating are those with borderline conditions, with whom it is necessary to employ the provocative tests. By one plan of management the patient is studied intermittently for twenty-four hours, and the data collected is voluminous.

It is thus obvious that a graphic tabulation of data may represent studies made every few minutes to every few months. It is probable that no ideal system of recording in graphic form can be presented which will be appropriate for all varieties of study.

From the Department of Ophthalmology, Long Island College Hospital.

In an effort to analyze data on glaucoma for study in graphic form, it has been found difficult to avoid confusion when many factors are plotted on a single sheet. The crossing of many curves and the confusion of a variety of symbols overlapping in significant areas may hide the very relation which one is seeking to render comprehensible.

It is obvious that the collected data, derived from various tests, are stated in totally different units of measure. They are nevertheless relatively coordinate. Tabulation of data is of little value unless it encourages rapid, accurate interpretation.

It was found that all data in figures fall between 0 and 300. I have tried numerous forms of tabulation and have discarded many systems of tabulating. The current form is presented in the accompanying illustration. It permits recording of the "occasional study" as well as recording of meticulously collected data from provocative testing.

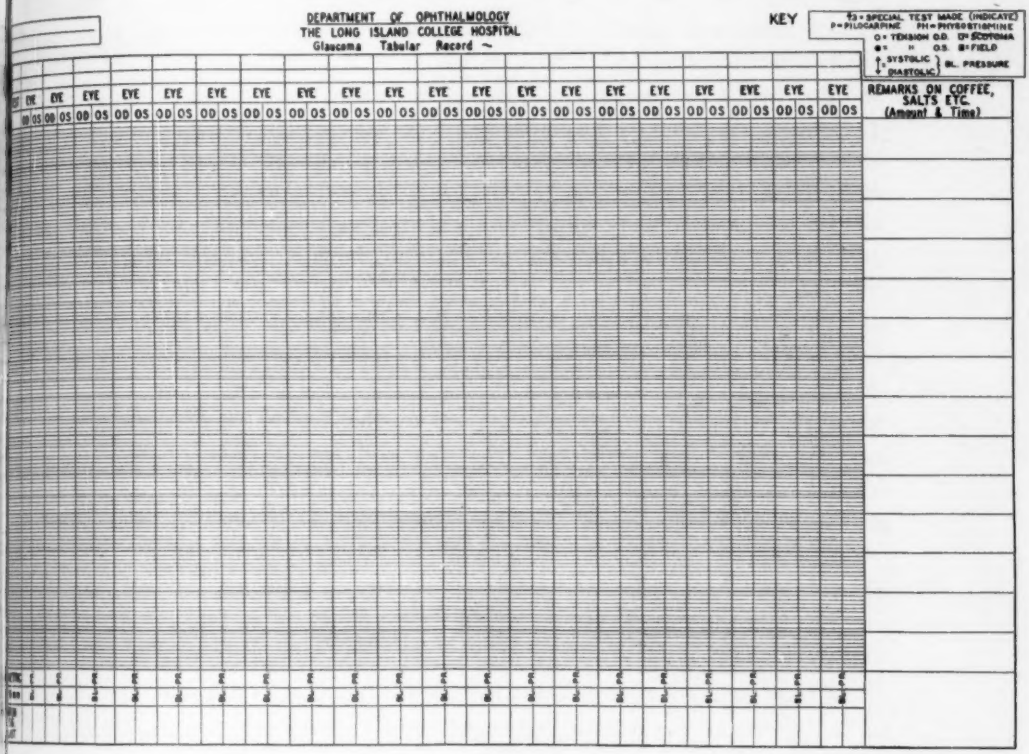
Directions for Use.—In the left hand column of the chart are placed the measurements as determined by the various methods of examination. These figures therefore represent different units for each test. Thus they represent pupillary diameter in millimeters (as determined by a pupillometer); they represent the denominator of the metric (or English) fraction expressing visual acuity (all fractions should be converted to read as though vision were taken at a distance of 6 meters, or 20 feet), they represent scotoma units or visual field units and they represent blood pressure and intraocular pressure by millimeters of mercury. (One should always note not only the instrument used but the model and the manufacturer's number.)

The symbols indicated in the key should be used. The specific test should be recorded in the column marked "Test" and connected by a dotted line to the first reading of the corresponding plotting. The tension symbols should be connected by lines, the record for the right eye by a continuous line and that for the left eye by a dotted line. The blood pressure should be indicated on the dotted line between the "O. D." and the "O. S." column by the symbols indicated in the key. The visual field and the scotoma can be measured by a conventional map measure [1] and recorded by the appropriate symbols, as indicated in the key. The map measure is a small instrument somewhat like a watch, with a wheel in the position of 6 o'clock.[2] By passing this wheel from above downward over the surface of the plotted defect, moving it 1 degree for each succeeding passage, one gets an arbitrary figure which is read off the dial of the instrument and which can be recorded as scotoma units. Should

1. For a more elaborate description of technic, see Evans, J. N.: An Introduction to Clinical Scotometry, New Haven, Conn., Yale University Press, 1930, p. 109.

2. Keuffel and Esser, Manufacturer.

a map measure not be conveniently at hand, one can take the vertical measurements 1 degree apart with the millimeter rule. When these measurements are added together the result will be the same as that secured with the map measure and is recorded not in millimeters but as scotoma units. Only the same predetermined significant area need be measured on each chart. If one prefers, small copies of the field charts may be pasted in the "Remark" column. All possible data on local and



Form for tabulation of data.

systemic medication should be recorded: not only the size of the dose, the concentration and the frequency but the time when the medication was last administered. The column headed "Remarks" is provided for the recording of general medication and for the elaboration of noteworthy data. Lengthy descriptions should be recorded on separate sheets. When provocative tests are made or special measures instituted, they should be indicated by a short arrow in the appropriate "Time" and "Eye" column and should be accompanied by a key number and reference in the "Remark" column.

Actual use of the form is much simpler than is evident from the written description. Both recording and reading are accurate and time saving.

II. PROVOCATIVE TESTS

SCHEDULE

The results of all provocative tests must be considered before one concludes that glaucoma is absent. It is dangerous to accept a negative result of a single test as conclusive. The history and the results of general physical and ophthalmologic examination must be included in the final data studied.

The first four studies are designed to establish the characteristics of the individual patient for comparison with the results of later tests and determination of the general trend of the diurnal curve. It would be ideal if many of these tests could be performed more frequently or other well known provocative tests could be added; but experience has shown that too many procedures upset the patient and there is also the danger of corneal traumatism from too frequent application of the tonometer.

The patient should be admitted to the hospital at 9 a. m. to be ready for the first test at exactly 10 a. m., all equipment being conveniently at hand so that no interference with the studies can occur. The patient should have had his usual breakfast, except that he should not have had tea, coffee or cocoa. Nor should he have had any alcoholic drink. He should not have taken a cathartic or other medication during the preceding twenty-four hours. Visitors must not be permitted, and all interruptions and nervous excitement must be guarded against. The patient should be moderately entertained, but not allowed to read.

The following materials should be ready, in good condition and constantly available:

1. Paper, colored pencils, an eraser and all chart forms and record sheets.
2. Properly illuminated (25 foot candles) and placed visual acuity charts (American Medical Association charts).
3. An appropriate campimeter, tangent screen or scotometer and occluder (if desired a standard perimeter also).
4. All orders written for numerous essentials and for coffee, water, etc.
5. Butyn sulfate in 2 per cent solution or other local anesthetic and a homatropine salt in 2 per cent solution.
6. A tonometer. The same standard instrument must be used throughout, as there are individual variations even in the same model.
7. A pupillometer with lights so arranged as to standardize the illumination.
8. A sphygmomanometer (mercurial) and a stethoscope.
9. An ophthalmoscope.
10. Other obviously necessary accessories.

Study 1.—This begins at 10 a. m.

A. The vision of each eye is recorded separately (preferably with the patient wearing his refractive correction).

B. The central visual field (angioscotometric) is plotted for each eye. (The peripheral visual field may also be plotted for each eye if desired, but the variations in this field are so slight as to be of little value in provocative testing.) A number of preliminary studies may be made by way of training.

C. Tonometric readings are taken for each eye, the make and the model of the tonometer and the manufacturer's number being noted.

D. The horizontal pupillary diameters are recorded. (Some form of pupillometer which will make allowance for the error of parallax is preferable.) Irregularity or other anomalies of the pupils should be noted. (This study should not be made until after the preceding studies, as the necessary light might modify results.) For the same reason study of the eyegrounds should be postponed until other ocular tests have been concluded.

E. The blood pressure (systolic and diastolic) should be taken with a mercury manometer.

F. All data should be recorded by the examiner. (All examinations should be made by the same person, preferably a physician.)

Study 2.—Begun at 1 p. m., this is a repetition of study 1, A through F.

Study 3.—Begun at 4 p. m., this is a repetition of study 1, A through F.

Study 4.—Begun at 7 p. m., this is a repetition of study 1, A through F.

Study 5.—The dark room test is performed from 9 to 10 p. m. Study 1 C is followed immediately by studies 1 B, 1 D, 1 E and 1 F. If the results are positive, a final study is made after the subject has gazed at a brightly illuminated wall for five minutes.

Study 6.—Begun at 1 a. m., this is a repetition of study 1, A through F.

Study 7.—Begun at 4 a. m., this is a repetition of study 1, A through F.

Study 8.—The water test is performed from 6 to 7 a. m. Study 1 is repeated in order A through F every fifteen minutes. The scotomas are charted as often as practical (at least once).

Study 9.—The coffee test is performed from 10 to 11 a. m. Study 1 is repeated, A through F, every fifteen minutes, with mapping of the scotomas as often as practical.

Study 10.—The mydriatic test is begun at noon. Study 1 is repeated, A through F, every half hour until 2 p. m., with plotting of the scotomas as often as practical.

Additional Tests.—The venous congestion test, the reading test, the decubitus test, the epinephrine test, the massage test and the paracentesis test may be substituted for those herein suggested but should not be added to them, for the reasons already cited.

TECHNIC

Dark Room Test.[3]—The patient is kept sitting up in a totally dark room for one hour, after which the studies are performed. A rise in tension of 15 mm. or more of mercury at this time is abnormal and as such is considered a positive result.

Water Test.—The patient drinks a quart (1 liter) of water rapidly. The studies are done every fifteen minutes. After forty-five minutes a rise of more than 8 mm. of mercury is abnormal. The blood and the urine can be checked for detection of abnormal dilution.

Coffee Test.—Two cups of coffee are drunk quickly or, if preferred, 0.2 Gm. of caffeine is injected intravenously. The studies are performed every fifteen minutes. A rise of tension of more than 15 mm. of mercury is abnormal. The rise in tension begins twenty to forty minutes after the coffee is taken and follows the rise in blood pressure.

Mydriatic Test.—A 2 per cent solution of a homatropine salt or, preferably, 2 per cent eucatropine hydrochloride solution is instilled. The studies are done every half hour. Any rise of tension is abnormal. This test is done only if all other tests give negative results. Any variation in the area of the scotoma (and in the blood pressure) is compared with the variation in tension. It will increase with a protracted rise of tension but may develop and recede at a different rate.

III. TESTS OTHER THAN PROVOCATIVE TESTS

Tests for glaucoma other than the provocative tests are often useful, and their results may be added to the chart.

Various therapeutic tests are of value in a consideration of the prognosis. The tests may be made before and after the patient has used the miotic treatment as prescribed, or at a single office visit one can make the studies before and one-half hour after instillation of a 0.5 per cent solution of physostigmine salicylate and repeat them one-half hour later. All provocative tests should be recorded in graphic form.

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3. This test is made after nightfall so as to insure complete darkness of the room, which might not be possible during daylight. I prefer that the patient be kept sitting up (head tipped back during application of the tonometer) for this test, as the result may be confused with the rise of tension which occurs in glaucomatous patients when they are reclining—the "decubitus" test. Some physicians prefer to combine these tests in order to exaggerate the effect of "darkness."

FLUORESCEIN TEST FOR CAPILLARY PERMEABILITY [4]

Technic.—The patient takes a capsule containing 25 cc.[5] each of fluorescein and sodium bicarbonate every fifteen minutes until 5 have been taken. He is then examined with the slit lamp. If there is undue permeability of the capillaries, the aqueous of the anterior chamber will take on a greenish color. If there is any doubt as to whether the stain has entered the anterior chamber the patient is asked to close one eye at a time and on opening it to look at a white background. If this appears yellowish or slightly green, it is positive that the fluorescein is mixed with aqueous although it may not seem so with the slit lamp.[6]

Prescription.—The following prescription is suggested:

	Grains	Gm.
Fluorescein	24	1.5
Sodium bicarbonate	24	1.5

Make 12 capsules.

Directions: Take 2 capsules every fifteen minutes until 10 have been taken.

Intravenous Use of Fluorescein.—Gifford [7] suggested the intravenous administration of fluorescein as being more reliable and more rapid.

Technic.—One gram of soluble sodium fluorescein [8] and 10 cc. of physiologic solution of sodium chloride are autoclaved for fifteen minutes and samples checked for toxicity and sterility by inoculation of rabbits.

Of this solution 10 cc. is slowly injected into an arm vein while the patient is seated at the slit lamp. The injection should take two to three minutes. The narrow beam or the pinhole beam of the slit lamp is used. The dye appears in the normal eye within three minutes (oblique illumination and a loupe can be used). The time when the injection is finished and that when a definite greenish color appears are taken.

23 Schermerhorn Street.

4. Though fluorescein is nontoxic, it is probably safer not to give it to patients suffering from nephritis.

5. Each capsule thus contains about 4 grains (0.26 Gm.).

6. In some instances the greenish tinge given the aqueous is exaggerated if a cobalt glass filter is placed in the illuminating system of the slit lamp.

7. Gifford, S. R.: Use of Fluorescein Intravenously as an Aid to Ophthalmic Diagnosis and Treatment, Arch. Ophth. **24**:122 (July) 1940.

8. Soluble sodium fluorescein powder is supplied by the National Analine Company.

INFLUENCE OF A CONSTRICTED PUPIL ON THE FIELD IN GLAUCOMA

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SAN FRANCISCO

The influence of the pupillary size on the field has found little consideration. In reviewing the standard works about perimetry and glaucoma I found only three short references to this subject. Traquair [1] wrote about the normal field: "The field may also be slightly diminished by a small pupil or increased by a large one if the test-object is very small, owing to the difference in the amount of light admitted to the eye. With moderately large test-objects the size of the pupil makes no appreciable difference." According to Peter,[2] "A large pupil will allow rays to fall farther forward on the retina than a contracted pupil." And in comparing the glaucomatous field on different occasions Duke-Elder [3] said that "every care should be taken to maintain constancy in the conditions, such as the degree of illumination, the size of the pupil, the time of the day and its relations to meals and stimulants, and the state of fatigue, excitement and anxiety." I do not recall any mention made in the casuistic literature; it is naturally impossible to read all the papers on glaucoma to be found in the ophthalmic literature.

I was impressed by the influence which the size of the pupil may have when I examined a patient (M. T.) whose right eye had glaucoma simplex. In spite of several operations for glaucoma performed elsewhere, vision in the left eye had been lost. In the preceding two years, during which he was under my observation, the function of the right eye remained the same and the tension was normalized by miotics; so conservative treatment seemed to be justified, the more as a cyclodialysis already had been performed and a trephine operation was indicated if further surgical intervention should be necessary.

The patient applied 1 drop of a solution of 0.3 per cent physostigmine salicylate and 0.5 per cent of a pilocarpine salt to each eye early in the morning and late in the evening and 1 drop of a 2 per cent pilocarpine

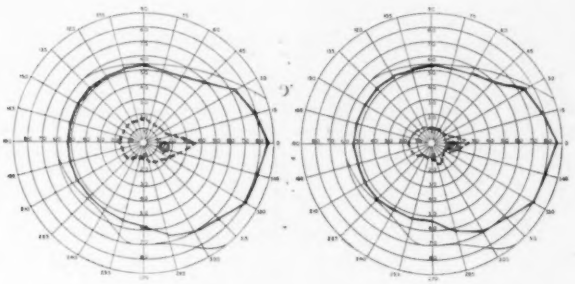
From the Department of Ophthalmology, Stanford University School of Medicine.

1. Traquair, H. M.: An Introduction to Clinical Perimetry, ed. 3, St. Louis, C. V. Mosby Company, 1938, p. 13.

2. Peter, L. C.: The Principles and Practice of Perimetry, ed. 4, Philadelphia, Lea & Febiger, 1938, p. 43.

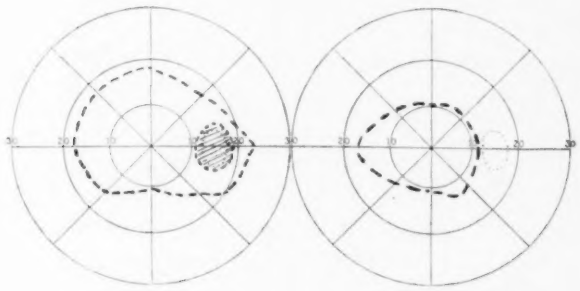
3. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 3384.

solution at noon and at 5 p. m. The field for a white 5 mm. test object at 300 mm. and the blindspot for a white 5 mm. test object at 1 meter were normal. Figure 1 *A* shows the markedly narrowed borders for a red 5 mm. object at 300 mm. The blindspot for a red 5 mm. object at 1 meter was enlarged to about one and a half times its normal size (fig. 2 *A*). It was certainly of great concern when one morning I found a further constriction for a red 5 mm. object at 300 mm. and a still more



A B

Fig. 1.—The visual fields of M. J. taken (*A*) July 24 and (*B*) July 23, 1941 at 8 a. m. The pupil measured 1.5 mm. when field *A* was taken and 0.75 mm. when field *B* was taken. The unbroken line shows the field for a white 5 mm. test object at 300 mm. and the broken line the field for a red 5 mm. object at 300 mm.



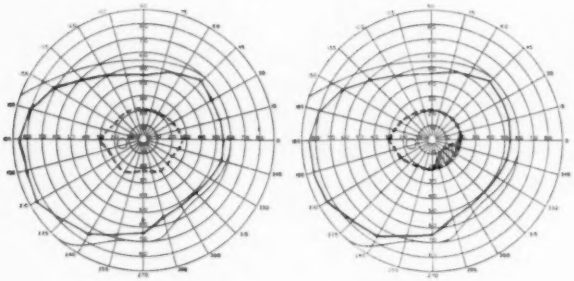
A B

Fig. 2.—The visual fields of M. J. taken (*A*) July 24 and (*B*) July 23, 1941 with a red 5 mm. test object at 1 meter. The pupil measured 1.5 mm. when field *A* was taken and 0.75 mm. when field *B* was taken.

marked change with the campimeter for a red 5 mm. object at 1 meter (figs. 1 *B* and 2 *B*), the narrowed borders no longer including the blindspot. When I noticed the pinpoint pupil of the patient—he had applied his physostigmine-pilocarpine drops one hour before—I asked him to come again the next morning without having instilled drops, and fortunately the field turned out to be the same as in previous months (figs. 1 *A*

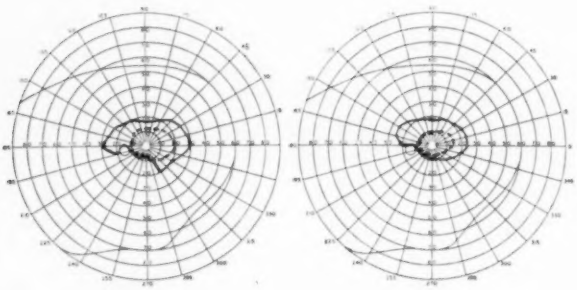
and 2 *A*). At intervals of two months the patient had been watched for two or three days, and until then I had always taken his field in the morning of the first day, when I examined his morning tension before the use of miotics.

To be sure that the change in the field caused by the miotic pupil was not a reaction peculiar to this particular patient, I examined several glaucomatous patients with field defects before and half an hour after



A B

Fig. 3.—The visual field of the left eye of a patient with glaucoma taken (*A*) at 9:30 a. m. and (*B*) 10 a. m. The unbroken line shows the field for a white 5 mm. test object at 300 mm. and the broken line the field for a red 5 mm. test object at 300 mm. The pupil measured 2.25 mm. when field *A* was taken and 1 mm. when field *B* was taken.



A B

Fig. 4.—The visual field of the left eye of a patient with glaucoma taken (*A*) at 9:30 a. m. and (*B*) 10 a. m. The unbroken line shows the field for a white 5 mm. test object at 300 mm. and the broken line the field for a red 5 mm. test object at 300 mm. The pupil measured 1.5 mm. when field *A* was taken and 0.75 mm. when field *B* was taken.

instillation of 1 drop of 0.5 per cent physostigmine salicylate solution; the pupil changed from about 2 mm. to about 1 mm. in diameter. Figures 3 and 4 both show a further narrowing of the already constricted field in physostigmine miosis. Figure 3 *B* reveals also a relative defect for a red 5 mm. test object at 300 mm.

The fact that even in a glaucomatous patient the normal field for white did not show any change made me expect that a normal field would remain practically the same after constriction of the pupil, a theory which was confirmed by the examinations. Only for a red 5 mm. object at 300 mm. and a white 1 mm. object at 300 mm. did the nasal field show a slight constriction, up to 2 degrees, in accordance with Traquair's quoted statement. In 1 patient, whose pupil changed from 4.5 to 1 mm. in diameter, the refraction was altered from emmetropia to myopia of 5 D. Particularly for small objects with the campimeter, a correcting glass had to be given; the change of refraction was likewise considered in the other patients.

The small size of the pupil in itself, as a mechanical obstacle, cannot have caused the change, because the much wider field for white stayed the same in the glaucomatous patients and the normal field practically did not change at all. The explanation is that the pinpoint pupil decreases the amount of light which falls on the retina, and, as the illumination diminishes, red becomes darker.[4] The diminished illumination and especially the darkening of red require an increase of ocular functional capacity, and apparently the slope which borders the already impaired glaucomatous field, particularly its nasal side, is so gentle and its level so low (according to Traquair's conception of the visual field) that the slightest change causes a recession of the borders, while the normal field, with its higher level and its steeper borders, is not affected.

As my patient shows, in estimating the progress of glaucoma and in assessing the treatment one might be misled by a change of field caused by a constricted pupil; to exclude this error it seems worth while to state the pupillary size on the visual field chart.

SUMMARY

Fields taken on different occasions may show a further constriction of an already narrowed field if taken when the pupil is small. This constriction may give the impression of "progressive" glaucoma and may lead to unnecessary therapeutic procedures. Consideration of the size of the pupil will eliminate this error in the evaluation of fields.

350 Post Street.

4. Hering showed that Purkinje's phenomenon is the consequence of an altered state of adaptation of the eye.

IDIOPATHIC MULTIPLE HEMORRHAGIC SARCOMA (KAPOSI)

REPORT OF AN UNUSUAL CASE IN WHICH THE INITIAL LESION WAS ON THE EYELID

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The following case of idiopathic multiple hemorrhagic sarcoma (Kaposi) is reported because of the unusual distribution of the lesions.

M. LaC., a white man aged 56, was first observed in the Dermatological Clinic of the New York Eye and Ear Infirmary on Nov. 9, 1937. He gave a history

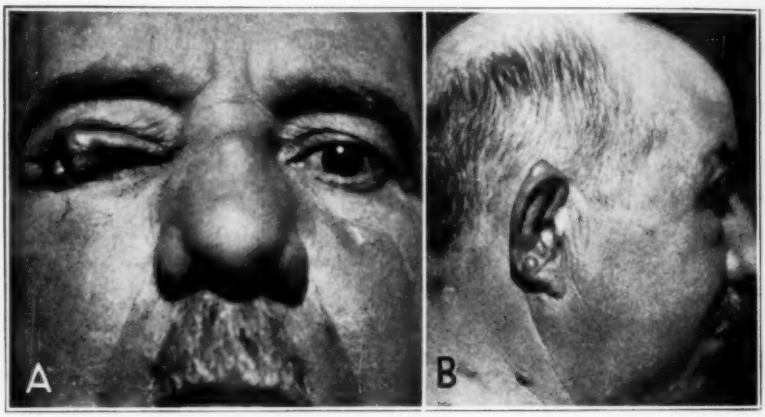

Fig. 1.—*A*, initial lesion, on the right upper eyelid. *B*, lesions which subsequently developed on the right ear, the chin and the neck.

of his eruptions having started eight months previously with a "growth" on the right upper eyelid. Subsequently there appeared similar lesions on the right lower eyelid, the right ear, the chin, the neck and the chest. Examination revealed a purplish elevated indurated nodule, 1.5 cm. in diameter, on the margin of the right upper eyelid adjacent to the outer canthus. This lesion protruded downward over the lateral third of the eyeball, making it impossible for the patient to approximate the eyelids. At the outer canthus of this eye and extending to the margin of the lower lid were two similar confluent nodules, each 0.5 cm. in diameter (fig. 1 *A*). There were also two nodules on the right ear: one, 0.7 cm. in diameter, on the anthelix adjacent to the lobule and the other, 1 cm. in diameter, on the uppermost part of the helix. There were fifteen other discrete and confluent lesions, varying in diameter from 0.3 to 1 cm., on the chin, neck and

From the Dermatological Clinic of the New York Eye and Ear Infirmary.

upper part of the chest (fig. 1 *B*). On the upper lateral aspect of the right thigh was a single lesion, 0.5 in diameter, of the same type. There were no other lesions on the lower extremities.

The family and the past history were irrelevant.

The Wassermann and the Kahn reaction of the blood were negative. The blood count showed 4,704,000 erythrocytes and 4,000 leukocytes, with 62 per cent

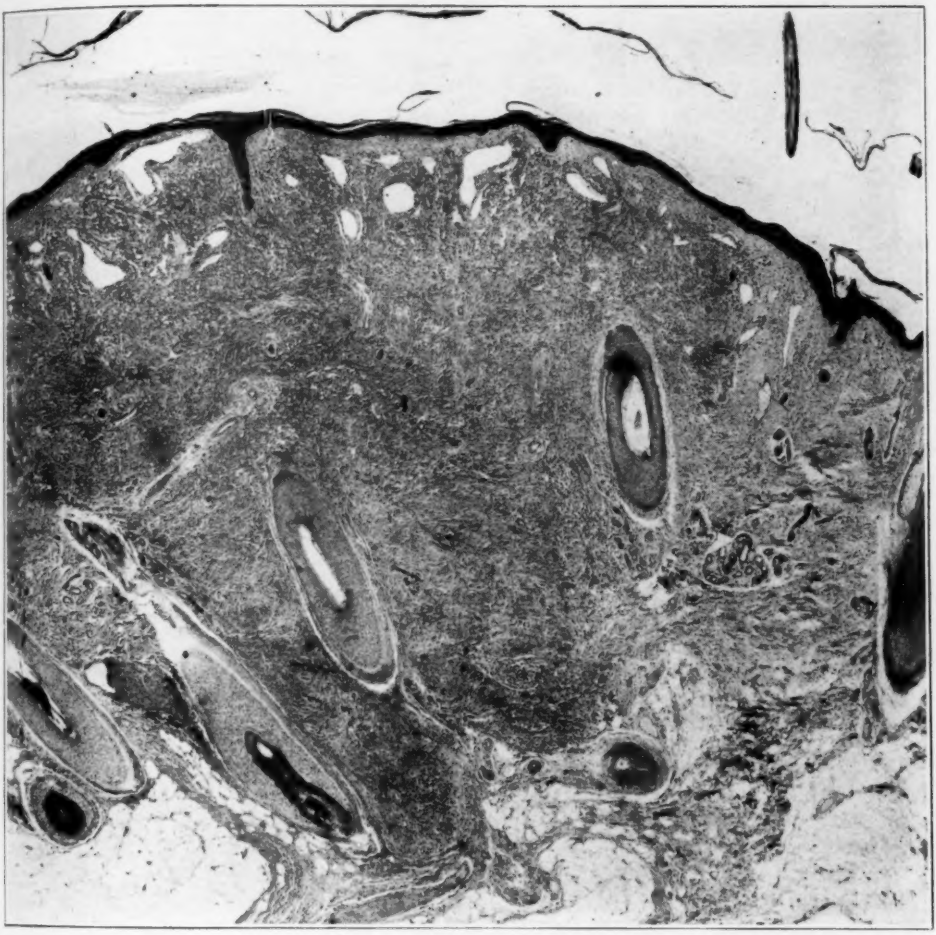

Fig. 2.—Low power photomicrograph of a section of the specimen from the lesion on the chest (× 25), showing hyperkeratosis, thinning of the epidermis and angiomatous changes in the corium.

polymorphonuclear neutrophils, 31 per cent lymphocytes and 7 per cent monocytes. Urinalysis gave no positive results. Microscopic studies, by Dr. Gerald F. Machacek, of sections from a biopsy specimen from a lesion on the chest corroborated the diagnosis of idiopathic multiple hemorrhagic sarcoma (Kaposi). The epidermis was thin and had undergone hyperkeratosis. Several large coarse

Fig. 3.—High power photomicrograph (× 220), showing an increase of spindle-shaped cells, foci of round cell infiltration and angiomatous changes in the corium.

hairs penetrated deeply into the corium. The corium showed a marked angiomatous change. The vessels varied greatly in size; many were large and there were numerous small, relatively thick-walled vessels (fig. 2). Fibrosis was present. An increase of spindle-shaped cells was noted, and foci of round cell infiltration were distinguished (fig. 3). Some of the deeper arteries showed markedly thickened walls. In the deeper portions of the section there were mononuclear phagocytes which contained a granular coarse brown pigment—hemosiderin.

The lesions responded to radium therapy. The patient was observed for three and a half years, during which several new lesions appeared on the face and neck but the extremities remained free except for the single small lesion on the upper lateral aspect of the right thigh. Metastases developed in the viscera, resulting in death on April 25, 1941.

COMMENT

Idiopathic multiple hemorrhagic sarcoma was originally described by Kaposi in 1897 under the name of idiopathic multiple pigment sarcoma. Kaposi had several cases under observation at that time and reported that the disorder invariably began on the hands and feet. Although the condition is a rare one, many examples have since been recorded. The following cases, which vary from instances of the classic form, originating on the hands and feet, have been found in a survey of the literature and represent only a small percentage of the total.

Gilchrist and Ketron [1] in 1916 reported a case of proved idiopathic multiple hemorrhagic sarcoma of eight months' duration limited to the face. There were six distinct lesions, which presented the typical clinical and histologic picture of this condition. Eight years later, however, Gilchrist [2] stated that in the course of a few years lesions on the hands and feet developed.

Radaeli [2] reported a case in which the initial lesion was on the nose and lesions subsequently developed on the extremities.

Traub [3] presented a case in which one of the earliest lesions, of four months' duration, was on the nose. It measured 2 cm. in diameter and was elevated above the cutaneous surface about 1.5 cm. Pea-sized pigmented vascular lesions were present on one ear and lip and on the dorsal surface of the fingers of one hand.

Guiffre [4] reported 2 cases of Kaposi's sarcoma, in 1 of which the cheek and ear were first attacked. A few months later, however, the eruption became generalized and involved the extremities.

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1. Gilchrist, T. C., and Ketron, L. W.: Report of Two Cases of Idiopathic Hemorrhagic Sarcoma (Kaposi), J. Cutan. Dis. **34**:429, 1916.

2. Cited by Kren.[5]

3. Traub, E. F.: Sarcoma-Kaposi, Arch. Dermat. & Syph. **17**:269 (Feb.) 1928.

4. Guiffre, M.: Sopra due casi di sarcomatosi telangectasica cutanea idiopatica generalizzata, Tumori **11**:336, 1925.

Kren [5] observed a case in which the first outbreak was in the submaxillary region, and he cited similar involvement in a patient of Lehner.

Mierzecki,[6] in a report of 7 cases, described 1 in which one auricle was entirely covered with nodules and there was an infiltration of similar color and character behind the ear. Other lesions were on the lower lip and both thighs. The hands and feet were not involved, with the exception of the right big toe, which was blue and swollen.

CONCLUSIONS

A case of idiopathic multiple hemorrhagic sarcoma (Kaposi) with the lesions limited to the right eyelids, right ear, chin, neck and chest, with a single small lesion on the right thigh, is reported. When first observed the primary lesion on the upper right eyelid had been present for eight months. Microscopic study of sections from a biopsy specimen confirmed the diagnosis. The patient was observed for three and a half years, during which time a few new lesions developed on the neck and chest but none on the extremities. He died as a result of metastases to the viscera.

A review of the literature revealed few cases in which the lesions of idiopathic multiple hemorrhagic sarcoma (Kaposi) did not appear first on the extremities. In almost all the rare instances in which the primary lesions have appeared on the face, lesions on the hands and feet have subsequently developed.

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5. Kren, O.: Sarcoma idiopathicum haemorrhagicum (Kaposi), in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, p. 891.

6. Mierzecki, H.: Sarcoma idiopathicum multiplex kaposi, Arch. f. Dermat. u. Syph. **165**:577, 1932.

INTERSTITIAL AND ULCEROUS KERATITIS IN LEISHMANIASIS

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Endemic and essentially tropical, leishmaniasis is known also as Biskra button, Aleppo button, Orient button, Bagdad button, Cairo button, Bauru ulcer and virulent wound of the Amazon.

In Africa its principal endemic centers are Biskra and Laghouat, Algeria; Tunis; Egypt; Morocco, and Ethiopia. In Oceania it is found in New Caledonia; in the Mediterranean region, in Crete and Cyprus, and in the Western Hemisphere, in Peru, Venezuela, the Guianas, the Antilles, Paraguay, Brazil and Argentina.

The parasite responsible is a protozoan which was identified in Brazil first by Lindenberg, of São Paulo, in 1904, and later by Pirajá da Silva, in 1911.

The transmitting insect of the disease is probably a phlebotomus.

My first observations on ocular leishmaniasis were in 1916, one of my assistants, Dr. Pedro da Costa, having in that year presented an interesting thesis on this subject before the medical faculty of Bahia.

Later, in 1932, we published a study of leishmaniasic keratitis in which we tried to explain the pathogenesis of its lesions, comparing them with the lesions of syphilitic keratitis.

The ocular lesions of leishmaniasis have been studied up to the present time only sketchily, not having been accorded even the most summary treatment in the textbooks of the specialty in spite of the frequency with which they occur in tropical countries. The lack is felt the more because, owing to the polymorphic aspect which the lesions present, they are likely to be confused in diagnosis with lesions due to different organisms.

The disease is ulcerous, granular, ulcerogranular, eczematoid, papillomatous or sclerotic, presenting a variety of forms equal to the variety of the tissues attacked, it being possible for the disease to appear in the skin as well as in the mucous membranes, cartilages, etc. It follows that it has an extremely variable course, which deserves study in its various forms of ocular localization.

Read at the First Pan-American Congress of Ophthalmology, Cleveland, Oct. 12, 1940.

My experience of nearly two decades in dealing with the ocular manifestations of leishmaniasis has afforded me ample opportunity to become familiar with certain details of the polymorphic aspect of the lesions, especially of the keratitis, which give rise to some doubt concerning the present conception of the pathogenesis.

In fact, if no doubt seems to exist that external autoinoculation occurs and gives rise secondarily to tegumentary, mucous or even corneal manifestations when the leishmaniasis is of the ulcerous, or vegetative, form, the same explanation cannot so readily be accepted for the rare form of keratitis without loss of substance, which has the appearance of diffuse infiltration similar to the parenchymatous, or interstitial, keratitis of hereditary syphilis.

The latter type of leishmaniasic keratitis is characterized by an inflammatory infiltration affecting the surface and the middle layers of the cornea without a tendency to attack the deeper layers, as is demonstrated by biomicroscopic examination.

In 1 case which came under my observation the grayish white infiltration, with a diffuse and asymmetric aspect, was located in the central zone and a little above the upper half of the cornea, fading as it approached the periphery, without one's being able to detect the least sign of interruption in the epithelial surface. A meticulous rhinoscopic examination, in the absence of external tegumentary lesions, revealed minute ulcers of leishmaniasis about 6 mm. in diameter situated in the highest and the front part of the nasal septum on the side corresponding to the ocular lesion. In another case, which was no less interesting, the patient presented an ulceration of the eyelid, including the mucous membrane, on the side of a keratitis of the interstitial type, without the least loss of epithelial substance, this finding having been carefully verified with the corneal microscope. Accompanying the ocular lesions there were other leishmaniasic manifestations, more or less extensive, located in the back and in the legs. Other observations previous to these disclosed the same order of circumstances, though without the corroboration of biomicroscopic examination.

It should be emphasized that in all the cases observed abundant proofs were given of the efficacy of specific treatment with antimony and potassium tartrate according to the Brazilian method of Gaspar Vianna, which confirmed the suspected causation. In view of the nature of the corneal lesions from the anatomic-pathologic point of view, it would not be logical to admit the possibility of Leishmania tropica as the etiologic agent without agreeing to the probable inoculation through the blood vessels or lymph ducts, which is contrary to the idea generally accepted at present, that is introduction of the parasite into the cornea exogenously or by external autoinoculation.

In fact, the cure simultaneously effected of the tegumentary lesions of the eyelid and the other lesions in which microscopic examination confirmed the presence of the parasite and of the interstitial keratitis, in the cases referred to, by means of intensive specific medication leads necessarily to acceptance of the same causation for the two sets of lesions and establishes a different pathogenic concept, at least so far as the interstitial form of leishmaniasic keratitis is concerned.

At any rate, what seems to be beyond question is that the existence of the parasite within the cytoplasm of the monocytes or of the polymorphonuclear cells is not necessary to its life in the human organism, for it is able to live in other surroundings, from which it may be carried by the blood or the lymph until localized, in the lesions under consideration, in the corneal tissue through the complex canalicular labyrinth of its elaborate structure.

Thus would be justified the concept of a pathogenic mechanism, barring the *via exogena*, of autoinoculation arising from open tegumentary lesions. The inflammatory corneal process is not, according to my opinion, a consequence of nutritive disturbances or the like but rather is a direct manifestation of leishmaniasis occasioned by the presence in loco of the parasite in the parenchyma of the cornea.

There is good reason to believe that the pathogenesis of interstitial leishmaniasic keratitis presents a perfect analogy with tuberculous, leprous and syphilitic keratitis when they appear with the same clinical aspect.

Biomicroscopic examination in 2 cases of interstitial leishmaniasic keratitis permitted confirmation of the presence of a slightly diffuse infiltration, there having been noted a slight exudation between the upper corneal layers by a confluence of movable corpuscles, or leukocytes, besides proliferation on a smaller scale of fixed cells. Little smoky patches, more or less confluent, irregular in outline, like plastic deposits, appeared in the zone of infiltration, denser at the center and rarer in the periphery, through which the nerves intertwined, visibly swollen and brilliant, in the form of silklike filaments. The vascular network, of relatively slight volume, was prominent at the edge, advancing in the direction of the infiltrated zone, where it formed a series of small curves. These decreased as they approached the epithelial surface without, however, emerging. In 1 of the cases, a little above the pupillary field between 2 and 3 o'clock there was a nodular formation, rounded and opalescent as seen with direct illumination, composed of an agglomeration of tiny points, which shut off the view of the iris. In general the zone of nodular infiltration grew thinner toward the periphery, and the finer vascular elements formed narrow strips, which disappeared in threadlike

branches, extending almost to the surface, while others were distributed more deeply, penetrating the middle layers of the cornea. The arterial capillaries were distinguished with perfect clearness on the surface plane, owing to their accentuated rhythmic contraction. In spite of the manifest tendency toward invasion of the entire thickness of the cornea by the whitish patches which reflected the initial infiltration, the deepest layers seemed to be entirely intact, including the endothelium, which was seen through strips of tissue still integral or but slightly affected by the infiltrating process. At the same time, the transparency of the aqueous humor afforded proof of its complete integrity. In fact, though using a narrow focus of light with maximum intensity, I was not able to detect any heterogenous elements which might cause the slightest alteration in the aqueous humor.

The interstitial keratitis of leishmaniasis recedes with much greater rapidity, relatively, than does that of hereditary syphilis, especially if the lesions are not deep and of long standing, although it is accompanied from the beginning by inflammatory symptoms more or less intense, such as pain, photophobia, lacrimation and hyperemia. The exudation and the spots, which have been well defined, disappear gradually under the influence of the specific and the local medication without leaving the traces of softening which give rise to the keratectasia frequently observed in the parenchymatous keratitis of the syphilitic or the tuberculous type.

The vascularization, perhaps because it is less intense, passes through a slower regressive process. In none of the cases which have come under my observation has there been a reaction in the uveal tract, causing serious complications, such as usually occurs with the syphilitic and other types of lesions.

The other form of leishmaniasic keratitis, certainly much more frequent, is the ulcerous, which in all the cases I have observed showed a direct relation to other lesions in the vicinity of the eye. In no case, however, did I see the typical phlyctena considered by some authorities to be the principal phenomenon, closely followed by a deep and general infiltration in the cornea. On the contrary, clinically the corneal localizations of leishmaniasis present little or nothing in particular except at times efflorescences, more or less acuminate, which rise in the field of the cellular infiltration and are accompanied not infrequently by a strong pericorneal reaction and accentuated subjective phenomena. It should, however, be made clear that these are not ordinary manifestations, for in the majority of cases the initial ulcerative process is characterized by erosion of the epithelium in the zone of circular or slightly eruptive opalescent spots, more condensed in the center of the infiltration, revealing the collection of the cellular elements of defense. In either case,

however, the ulceration behaves more or less in the manner of the ulcerous lesions common in the cornea, having no distinctive special characteristics.

After staining the ulcerated zone with methylene blue, one notes, by means of the corneal microscope, on a grayish blue, irregular background, composed of strongly infiltrated tissue, an accumulation of cellular elements plainly in a state of disintegration. Surrounding the ulceration can be seen deep as well as superficial vessels in which the red cells, completely paralyzed, form solid columns.

The vascularization around the ulceration is undoubtedly much less extensive, although made up of more substantial vessels, than that noted in the interstitial form. The pericorneal vascularization, on the contrary, is much more intense in the ulcerous form and is accompanied by inflammatory phenomena, which also are more violent. From the sides of the ulceration there emerge grayish streaks which extend discretely in the direction of the sound and still transparent tissue. In some places the infiltration extends beyond the limits of the ulcerated zone, looking like small diverticula, without, however, reaching far.

The regression of the lesions depends naturally on their gravity and extension, a *restitutio in integrum* being rare, for they easily increase in depth, often reaching Descemet's membrane and giving rise to keratectasia or to perforations.

TREATMENT

The treatment of leishmaniasis cannot fail to be of interest to the ophthalmologist, on account of the frequency and the gravity of ocular manifestations. Since the armamentarium possesses a medicine truly specific, which has already been amply discussed, one is amazed to see in the foreign publications references to cures obtained with arsenicals and other substances of doubtful value.

The Brazilian method, discovered by Gaspar Vianna, comprising injections of antimony and potassium tartrate, is a specific, none other having the advantage of it in simplicity, in duration or in practical results.

The preferred route of injection is the intravenous.

I employ a 2 per cent solution of the tartrate in double-distilled water or in physiologic whey, injecting initially 2 cc. The dose may be increased to 12 or 15 cg., principally in cases of interstitial or ulcerous keratitis or of the grave forms of tegumentary ulceration of the eyelids.

In certain cases I prefer to use smaller doses repeated at shorter intervals.

The treatment should be intensive and as regular as possible to prevent the development of resistance to the drug by the organism. It

should be continued for some time after cure, to prevent recurrence of the disease.

The reactions sometimes provoked by intravenous injection of the drug are generally immediate or episodic and are characterized by headache, arthralgia, fever, diarrhea, tremor and, above all, violent coughing and anginal sensations.

All these manifestations disappear immediately on use of epinephrine and calcium chloride. It is necessary, at times, however, to diminish the dose of the tartrate.

As substitutes fuadin and other medicines have been employed.

A powerful auxiliary in the cicatrization of the ulcerous tegumentary lesions, including those of the eyelids, is ultraviolet irradiation, which I have employed with excellent results.

Clinical Notes

NEW CORNEOSCLERAL SUTURE TECHNIC

CARROL L. WEEKS, M.D., LOS ANGELES

Good results with any technic involving the placement of corneoscleral sutures lie in the operator's ability to profit by repetition; however, in my opinion the faults are exceedingly difficult to iron out. The placing of sutures prior to section, as in the technic of Kalt,[1] Liégard,[2] Mendoza,[3] Baldino,[4] Lindner,[5] Walker,[6] Verhoeff[7] and McLean,[8] demands dexterity in completing the section through the prepared tract or between previously placed sutures.

This dexterity with a cataract knife is not a constant, and for that reason I present a method which has enabled me to circumvent its lack.

As so ably described by McLean:

> The ideal suture for closing cataract wounds should be inserted in solid corneal and scleral tissue and not in loose, yielding conjunctiva. It should be placed before the section is made (completed) and should not require extensive manipulations after the eye is opened. It should go through, not over, the lips of the wound so as to give firm closure without danger of inversion of the edges, and it should be so placed that when tied it will bring the tissues back to exactly the preoperative position.

McLean added that the entire wound should be covered by conjunctiva as an added protection and for better surgical closure. "The method should not be too complicated for the average surgeon."

In my experience the correct placing of corneoscleral sutures, to obtain perfect apposition of the wound edges, seems dependent on the

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Read before the Los Angeles Society of Ophthalmology and Otolaryngology Feb. 23, 1942.

From the Department of Surgery of the University of Southern California School of Medicine.

1. Kalt, E.: On the Corneal Suture in Cataract Extraction, Arch. Ophth. **23**:421, 1894.

2. Liégard, H.: Une modification aux procédé de suture de la cornée dans l'opération de la cataracte, Ann. d'ocul. **149**:119, 1913.

3. Suarez de Mendoza: Nouveaux faits de suture de la cornée dans l'opération de la cataracte, Bull. et mém. Soc. franç. d'opht. **10**:63, 1892.

4. Baldino, S.: Sutura corneale perfezionata, Rassegna ital. d'ottal. **4**:538, 1935.

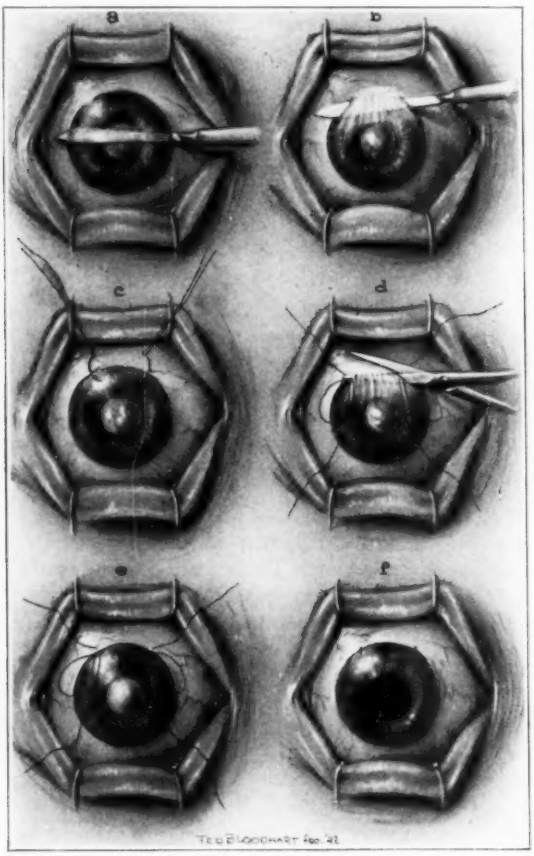
5. Lindner, K.: Ueber Abänderungen der intracapsularen Staroperation, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **52**:392, 1938.

6. Walker, C.: Exactly Appositional Sutures in the Cataract Operation, Tr. Am. Ophth. Soc. **27**:51, 1929.

7. Verhoeff, F. H.: A Corneo-Sclero-Conjunctival Suture in Operations for Cataract, Tr. Am. Ophth. Soc. **25**:48, 1927.

8. McLean, J. M.: New Corneoscleral Suture, Arch. Ophth. **23**:554 (March) 1940.

sharpness and smallness of the needle and the dexterity of the surgeon. No corneoscleral suture can be well placed without good light and good magnification. The mechanics of a properly placed corneoscleral suture involve both direction and depth. The suture directed obliquely away from an imaginary line toward the center of the cornea will tend to exert a pull which disturbs the apposition of the wound lips even though there was apparent perfect apposition before the tie was completed. A



Technic for placing corneal sutures.

through and through suture is also objectionable, in that the wound edges may invert or overlap and thus make possible the epithelization of the anterior chamber, whereas if the depth is gaged to include only half the thickness of the scleral and the corneal lips the wound apposition is faultless. Epithelial ingrowth is rare with any type of suture if proper care is taken in the wound toilet prior to closure.

The following method was evolved for purposes of safety in dealing with complicated cataract, glaucoma when a previous operation has been

performed and there are filtering scars and a routine lens extraction with or without a round pupil. The method may be utilized without a conjunctival flap, i. e. in a strictly corneal section, or with a conjunctival flap, i. e. in a corneoscleral section.

The accompanying illustration is self explanatory; however, a description of the technic follows:

In a strictly corneal section (one without a conjunctival flap), after the usual preparation and cocainization of the eye, followed by akinesia and retrobulbar injection if used, the lid is retracted with a speculum or other appliance. External canthotomy is performed if necessary. The eye is then fixed; puncture and counterpuncture are done with a cataract knife; the section is carried upward but not to completion, being stopped short without turning, to leave an intact corneal bridge 2 to 4 mm. above, and the knife is withdrawn. In a strictly corneal section there will be no bleeding. After the knife is withdrawn without depression or elevation, the chamber will not entirely collapse. A small sharp iris hook is then inserted in the upper margin of the section and slid upward to engage the extreme edge of the uncut bridge. This maneuver affords firm traction for introduction of a corneoscleral suture, which is placed through the wound lips immediately behind the hook. Both the scleral and the corneal lips may be engaged with one sweep of the corneal needle. The suture is pulled through and the loop so arranged as to provide easy access for later cutting of the bridge, iridectomy and extraction of the lens. The hook is disengaged and reinserted at the other margin of the bridge and the procedure repeated for insertion of the second corneoscleral suture. Cutting of the bridge is accomplished by flat scissors in the plane of the original section. The remainder of the extraction is according to the operator's choice.

When there is a conjunctival flap, the flap is dissected downward and smoothed over the cornea and the section carried out as described, being stopped short of completion to allow a corneoscleral bridge of approximately 2 to 4 mm. Sutures are then inserted after the method of McLean by starting through the conjunctiva, reversing the needle to engage the wound lips immediately adjacent to the intact corneoscleral bridge and close to the hook placed at the end of the bridge and finally emerging through conjunctival flap. The two loops are then laid aside and the second suture applied like the first. The corneoscleral bridge is then severed by scissors. If the flap is dissected upward from the corneoscleral margin after the method of Verhoeff,[7] the section and sutures work equally well.

SUMMARY

By this method corneoscleral sutures are placed while the eye has the protection of the intact corneoscleral bridge above.

Exact apposition is obtained by insertion of the sutures through the section wound immediately adjacent to the intact corneal bridge.

The procedure may be carried out either with or without a conjunctival flap.

The two sutures are optimally placed and sufficient.

2007 Wilshire Boulevard.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

OPHTHALMIC REQUIREMENTS OF THE MILITARY SERVICES

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NEW ORLEANS

The fundamental information in this review has been compiled on request of the American Committee on Optics and Visual Physiology. Its purposes are (1) to help ophthalmic military examiners quickly find desired information; (2) to promote, especially among ophthalmologists, a better understanding of current military regulations concerning visual function, and (3) to help those interested obtain supplementary information through authoritative publications and keep informed concerning changes in pertinent regulations.

Only if ophthalmologists have the correct information themselves can they approach intelligently the many questions asked them by their patients regarding the ophthalmic requirements of the military services. Also, compilations of this kind will tend to standardize visual requirements in all branches of the service. Through them, slight ambiguities and inconsistencies can be more easily avoided.

For each branch of the service—Selective Service, Army, Navy, etc.—section 1 of the compilation is devoted to minimum requirements, section 2 includes qualifying and disqualifying diseases and conditions and section 3 contains the sources of specific information.

SELECTIVE SERVICE: ARMY

SECTION 1.—Class 1-A consists of selectees fit for unlimited service; class 1-B, of selectees fit for limited service, and class 4, of selectees unfit for military service. The minimum functional requirements are as follows:

	Vision			
	Without Glasses		With Glasses	
Classification	One Eye	Other Eye	One Eye	Other Eye
Class 1-A..... (authority 1, par. 16)	20/200	20/200	20/40	20/40
Class 1-B, enlisted personnel (authority 1, par. 17)	(*a*) 20/400	20/400	(*a*) 20/400 to 20/40	20/40
	(*b*) Blindness, disease not progressive	20/200	(*b*) Blindness, disease not progressive	20/40

From the Department of Ophthalmology, Medical Center, Louisiana State University School of Medicine.

Classification	Vision			
	Without Glasses		With Glasses	
	One Eye	Other Eye	One Eye	Other Eye
Officers of the supply arms and services (authorities 3, 4, 5)	(*a*) Any degree	Any degree	(*a*) 20/40; no organic disease	20/20
	(*b*) To blindness	20/200	(*b*) Below 20/40; no organic disease	20/20; no history of disease in more defective eye which might involve better eye; satisfactory prosthesis in cases of ophthalmostereosis
	(*a*) Complete color blindness not disqualifying (*b*) Correcting glasses must be in possession of examinee (authority 4)			
Class 4..... (authority 1, par. 18)	(*a*) Less than 20/400	20/400	Less than 20/400	20/40
	(*b*) Blindness	20/200	Blindness	20/40

SECTION 2.—The qualifying and disqualifying conditions and diseases are as follows:

	Qualifying for:		Disqualifying for:
	Class 1-A	Class 1-B	Classes 1-A and 1-B *
Lids	Slight adhesions to eyeball	1. Slight inversion 2. Slight eversion 3. Ptosis 4. Slight trichiasis 5. Chronic slight blepharitis 6. Blepharospasm	1. Disfiguring cicatrices 2. Lagophthalmos if associated with hyperthyroidism
Lacrimal apparatus		1. Slight epiphora 2. Slight chronic dacryocystitis	
Orbits	Slight exophthalmos provided hyperthyroidism is excluded	Loss of one eye or blindness in one eye with vision in other eye of not less than 20/200 corrected to not less than 20/40	Pronounced exophthalmos
Muscles	1. Slight nystagmus 2. Strabismus which does not interfere with vision	Mild diplopia involving one eye only (paralysis of muscles of one eye)	1. Marked nystagmus 2. Paralysis of extrinsic ocular muscles unless mild
Conjunctiva	1. Slight conjunctivitis 2. Chronic simple conjunctivitis if remediable	Chronic conjunctivitis	1. Disfiguring cicatrices 2. Trachoma
Cornea	Small pterygium	1. Superficial ulcer provided acceptance is deferred until ulcer is healed without diqualifying impairment of vision 2. Pterygium, extensive	1. Disfiguring cicatrices 2. Chronic keratitis 3. Chronic recurrent inflammatory disease of globe 4. Deep chronic ulcer 5. Trachoma

	Qualifying for:		Disqualifying for:
	Class 1-A	Class 1-B	Classes 1-A and 1-B*
Sclera	Not mentioned in regulations	Not mentioned in regulations	Chronic recurrent inflammatory disease of globe
Iris and ciliary body	Iridectomy if vision is within minimum standard requirements	Not mentioned in regulations	Not mentioned in regulations
Lens	Not mentioned in regulations (see visual requirements)		
Choroid	Not mentioned in regulations	Not mentioned in regulations	Any active disease
Retina	Color blindness	Not mentioned in regulations	1. Any active disease 2. Detachment
Optic nerve and visual portion of brain	Color blindness	Not mentioned in regulations	1. Any active disease 2. Abnormal conditions of eyes due to disease of brain
Miscellaneous; glaucoma; operation	Conditions due to iridectomy or other operation on eye if condition for which operation was performed has been relieved and vision is within or above minimum standard requirements (authority 1, par. 16)	Not mentioned in regulations	1. Vision less than minimum requirements for special and limited military service 2. Glaucoma

* Disqualification for classes 1-A and 1-B automatically places the selectee in class 4.

SECTION 3.—The authorities for the ophthalmic requirements of the Selective Service as it pertains to the Army are as follows:

1. Standards of Physical Examination During Mobilization, Mobilization Regulations 1-9, United States War Department, Aug. 31, 1940, sect. 4, par. 15-20.
2. Circular 110, United States War Department, Oct. 4, 1940, par. 1.
3. Letter AG 210.31 (12-19-41).[5b]
4. Letter RP-A, Jan. 7, 1942.[5b]
5. Waiver of Physical Defects for Limited Service Officers, Medicine and the War, J. A. M. A. (*a*) **118**:1146 (March 28) 1942; (*b*) **119**:270 (May 16) 1942.

SELECTIVE SERVICE: NAVY

As of May 15, 1942 all selectees are primarily examined by the Army. Specific Selective Service regulations will be issued by the Navy when required.

ARMY

SECTION 1.—The functional requirements for the Army are as follows:

	Vision						Muscles		
	Without Glasses		With Glasses						
	One Eye	Other Eye	One Eye	Other Eye	Refraction	Color Vision	Esophoria	Exophoria	Hyperphoria
1. Enlisted personnel: (*a*) Regular Army (*b*) National Guard (*c*) Men of National Guard inducted into federal service (*d*) Army of United States (A. U. S.) (authority 6, sect. 1) (authority 3, par. 16)	20/100	20/100	20/40	20/40	Not mentioned in regulations	Color blindness permitted (authority 3, par. 16)	Not mentioned in regulations		
2. Commissioned officers of Regular Army except (authority 7):	20/40	20/40	20/20	20/30	Not mentioned in regulations	Must distinguish red and green; Holmgren's or equivalent test (except chaplains' corps)	Not mentioned in regulations		
3. Judge Advocate General's Department, Medical Corps, chaplains, officers of National Guard and Organized Reserve and officers of Army of United States (authority 7)	20/100	20/100	20/20	20/30					
Military Academy	20/30	20/30	20/20	20/20	With cycloplegic, +2 D. sph. or less or —0.75 D. sph. or less in each eye	Must distinguish red and green in Holmgren's or equivalent test without confusion	Less than: 10 Prism diopter	5	1
	Not more than 2 D. of hyperopia or 0.75 D. of myopia permitted (authority 8)								

SECTION 2.—The disqualifying conditions and diseases for all branches of the Army are as follows (authority 1, section 3, paragraph 17):

1. Lids	Destruction of lids, cicatrices, adhesions, inversion, eversion, lagophthalmos, trichiasis, ptosis, blepharospasm, chronic blepharitis, malignant tumors
2. Lacrimal apparatus	Epiphora, chronic dacryocystitis, lacrimal fistula
3. Orbits	Loss of one eye, pronounced exophthalmos
4. Muscles	Pronounced nystagmus, well marked strabismus, diplopia
5. Conjunctiva	Cicatrices, chronic conjunctivitis, trachoma
6. Cornea	Chronic keratitis, ulcer, staphyloma, opacities reducing vision below requirements, cicatrices, pterygium, trachoma, xerophthalmos
7. Sclera	Not mentioned in regulations
8. Iris, ciliary body	Irregularities in form of iris, coloboma, synechia, iritis, absence of pigment, tumor
9. Lens	Opacities reducing vision below requirements
10. Choroid	Coloboma, choroiditis, tumor
11. Retina	Retinitis, neuroretinitis, detachment, night blindness, tumor
12. Optic nerve, visual portion of brain	Neuroretinitis, optic neuritis, atrophy of optic nerve, night blindness, abnormal conditions of eye due to disease of brain
13. Miscellaneous	Glaucoma, asthenopia, visual functions below requirements

SECTION 3.—The authorities for the ophthalmic requirements of the Army are as follows:

1. Medical Department: Standards of Physical Examination for Entrance into Regular Army, National Guard and Organized Reserves, Army Regulations 40-105, United States War Department, May 29, 1923, sect. 3, par. 15-18.
2. Medical Department: Standards of Physical Examination for Entrance into Regular Army, National Guard and Organized Reserves, Army Regulations 40-105, Changes 5, United States War Department, Aug. 17, 1940.
3. Standards of Physical Examination During Mobilization, Mobilization Regulations 1-9, United States War Department, Aug. 31, 1940, sect. 4, par. 15-20.
4. Medical Department: Standards of Miscellaneous Physical Examination, Army Regulations 40-100, United States War Department, Sept. 10, 1940, par. 1-19.
5. Circular 110, United States War Department, Oct. 4, 1940.
6. Circular 117, United States War Department, Oct. 18, 1940.
7. Circular 229, United States War Department, Oct. 30, 1941.
8. Letter of the Surgeon General, Jan. 27, 1942. "The visual acuity requirement for admission to West Point has been lowered to 20/30 in each eye without glasses, corrected to 20/20 in each eye."

NAVY AND MARINE CORPS

SECTION 1.—The functional requirements of the Navy and the Marine Corps are as follows:

	Vision				Color Vision
	Without Glasses		With Glasses		Tests Conducted with Pseudo-isochromatic Plates for Testing Color Perception; American Optical Company or Stillings Test
	One Eye	Other Eye	One Eye	Other Eye	
1. Enlisted personnel..... (authority 1*b*, sect. 4, par. 1428)	15/20	15/20	20/20	20/20	Must read one plate of each of the following groups: (1) plates 1, 2, 3, 4; (2) plates 7, 8, 9, 10, 13, 14 and (3) plates 17, 18, 19, 20; these groups are represented in Stillings twentieth edition * by plates 3, 4 and 8 (authority 3)
2. Commissioned officers, line of Navy and Marine Corps	18/20	18/20	20/20	20/20	Must complete one of the two tests
3. Commissioned officers (staff), civil engineers, Supply Corps, Medical Corps, Dental Corps, Chaplain Corps and line officers of Reserve Corps doing staff duty, such as engineers, naval constructors, and legal and professional specialists (authority 2)	12/20	12/20	20/20	20/20	Must complete one of the two tests
4. Naval Academy.....	20/20	20/20	No myopia or myopic astigmatism with eyes under homatropine cyclopiegia		Must complete one of the two tests
5. Naval Reserve Officers Training Corps and V-7 enlisted personnel	18/20	18/20	20/20	20/20	Must complete one of the two tests

* Stilling, J.: Stillings pseudo-isochromatische Tafeln zur Prüfung des Farbensinnes, ed. 20, Leipzig, G. Thieme, 1939. This edition cannot be purchased in the United States. Two editions based on but not identical with it were published in this country in 1940, one by the American Optical Company, Southbridge, Mass., and the other by E. B. Meyrowitz Surgical Instrument Company, Inc., New York.

SECTION 2.—The disqualifying conditions and diseases for the Navy and the Marine Corps are as follows (authority 1 *b*, paragraph 1429):

1. Lids	Destruction of lids, disfiguring cicatrices, adhesions, inversion, eversion, lagophthalmos, trichiasis, ptosis, blepharospasm, chronic blepharitis, malignant tumors
2. Lacrimal apparatus	Epiphora, chronic dacryocystitis, lacrimal fistula
3. Orbits	Loss or disorganization of one eye, pronounced exophthalmos
4. Muscles	Pronounced nystagmus, marked strabismus, diplopia
5. Conjunctiva	Cicatrices, chronic conjunctivitis, trachoma
6. Cornea	Chronic keratitis, ulcer, staphyloma, opacities reducing vision below requirements, cicatrices, pterygium, trachoma, xerophthalmos
7. Sclera	Not mentioned in regulations
8. Iris, ciliary body	Irregularities in form of iris, coloboma, iritis, albinism, tumor
9. Lens	Opacities reducing acuity of vision
10. Choroid	Choroiditis, coloboma, tumor
11. Retina	Retinitis, neuroretinitis, detachment of retina, night blindness, tumor
12. Optic nerve, visual part of brain	Neuroretinitis, optic neuritis, atrophy of optic nerve, night blindness, abnormal conditions of eye due to diseases of brain
13. Miscellaneous	Glaucoma, asthenopia, visual functions below requirements

SECTION 3.—The authorities for the ophthalmic requirements of the Navy and the Marine Corps are as follows:

1. Physical Examinations for the Medical Department of the United States Navy, Reprint of Chapter 11, Manual of the Medical Department, 1938, (*a*) sect. 1, par. 1401-1407; (*b*) sect. 4, par. 1426-1432.
2. Recruiting Circular Letter, no. 130-41, P14-4/A2-11 (635), United States Navy Department, Bureau of Navigation, Dec. 4, 1941.
3. Form Letter no. 12, A2-2/EN-10 (113-38), Department of the Navy, Bureau of Medicine and Surgery, Oct. 28, 1941.

COAST GUARD

Future regulations will be issued by the Navy when required. Ophthalmic examinations were formerly under jurisdiction of the United States Public Health Service, whose regulations are here given:

SECTION 1.—The functional requirements have been as follows:

	Vision				
	Without Glasses		With Glasses		
	One Eye	Other Eye	One Eye	Other Eye	Color Vision
1. Applicants for enlistment.....	20/30	20/30	20/30	20/30	Normal color vision required
2. (*a*) Cadets for appointment as ensigns. (*b*) Candidates for original commission as constructor, district commander or chief warrant officer	20/30	20/30	20/20	20/20	Normal color vision required; Ishihara test
3. Candidate for appointment as cadet	20/20	20/20	20/20	20/20	Normal color vision required

SECTION 2.—The disqualifying conditions and diseases have been practically the same as those for the Army and the Navy.

SECTION 3.—The authority for the ophthalmic requirements for the Coast Guard under the Treasury Department has been "Instructions for Medical Officers, Relative to Physical Examinations, United States Coast Guard, 1935" (United States Treasury Department, Public Health Service, 1935).

AIR CORPS: ARMY AND NAVY

Physical examinations in all branches of the Air Corps are given only by specially trained and qualified examiners. This section has, therefore, been condensed because of its limited use to the majority of readers.

SECTION 1.—Air Corps ophthalmic requirements in the Army and the Navy, which includes the Marine Corps and the Coast Guard, are basically similar. Specific differences are mentioned in detail in the following tabulation, which combines the functional requirements of all branches of the Air Corps:

I. Classification of personnel

A. Army, class 1 (authority 1 *a*)

1. Applicants for flying training
2. Rated senior pilots
3. Pilots
4. Combat observers
5. Balloon pilots
6. Senior balloon pilots
7. Balloon observers

B. Navy (authority 2 *b*)

Class 1, pilots

1. Pilots with less than twenty years of service
2. Pilots with twenty to thirty years of service; same requirements as given hereafter except that vision must be 10/20 in each eye without glasses and 20/20 in each eye with glasses
3. Pilots with thirty years or more of service; same requirements as given hereafter except that vision must be 8/20 in each eye without glasses and 20/20 in each eye with glasses

Class 2, other flying personnel

1. Student naval aviators
2. Naval aviators (airship)
3. Student naval aviators (airship)

Class 3, nonflying personnel

1. Naval aviator observers
2. Naval flight surgeons
3. Student naval flight surgeons (vision without glasses 15/20 in each eye)
4. Antiaircraft and aircraft machine gunners

II. Functional requirements for class 1 of Army and classes 1 to 3 of the Navy
Vision without glasses (glasses not permitted): each eye 20/20
Refraction with cycloplegic

Army: each eye less than + 1.5 D. sph. or + 0.5 or — 0.5 D. cyl.

Navy: each eye less than + 2.0 or — 0.5 D. sph. or + 0.5 or — 0.5 D. cyl. (authority 2 *b*)

Field of vision: Less than 15 degrees of contraction in any meridian

Color vision: Completion of Ishihara or Stilling and Holmgren tests

Depth perception: at 6 meters, 30 mm. limit (Howard-Dolman apparatus)

Muscles, extrinsic

Heterotropia, none

Esophoria

1. Less than 10 D.
2. Less than 4 D. when associated with prism divergence less than 4 D.

Exophoria: Less than 5 D.

Hyperphoria: Less than 1 D.

Red lens test for diplopia: no diplopia within 50 cm. in any meridian

Power of divergence: less than 15 and more than 3 D.

Angle of convergence: more than 40 degrees calculated from the formula $\frac{\frac{1}{2}\ \text{Pd} \times 100}{\text{PcB}} + 3$, in which Pd is the interpupillary distance and PcB the distance from the near point of convergence to the base line connecting the centers of rotation of the eyes (authority 1 *b*)

Accommodation: less than 3 D. below normal for age.

III. Classification of personnel: Army, class 2 (authority 1 *a*)

1. Rated senior pilots
2. Pilots
3. Combat observers
4. Balloon pilots
5. Senior balloon pilots
6. Balloon observers, provided their training and experience in the opinion of the chief of the Air Corps compensates for the lower physical standards of class 2

IV. Functional requirements for class 2 of the Army (authority 1 *b*)

Vision without glasses: each eye 20/40

Vision with glasses: each eye 20/20

Refraction: each eye less than + 1.5 or — 1.5 D. spher. or + 0.5 or — 0.5 D. cyl. (with cycloplegic)

Field of vision: less than 15 degrees of contraction in any meridian

Color vision: Completion of Ishihara or Stilling and Holmgren tests

Depth perception: at 6 meters, 35 mm. limit (Howard-Dolman apparatus)

Muscles, extrinsic (authority 1 *b*)

Heterotropia: none

Esophoria:

1. Less than 10 D.
2. Less than 4 D. when associated with prism divergence less than 4 D.

Exophoria: less than 5 D.

Hyperphoria: less than 1 D.

Red lens test for diplopia: no diplopia within 50 cm. any meridian

Power of divergence: less than 15 D. and more than 3 D.

Angle of convergence: more than 40 degrees calculated from the formula $\frac{\frac{1}{2}\ \text{Pd} \times 100}{\text{PcB}} + 3$, in which Pd is the interpupillary distance and PcB the distance from the near point of convergence to the base line connecting centers of rotation of the eyes

Accommodation: not less than 3 D. absolute; glasses for near vision required while flying and ability to read test at 50 cm.

V. Classification of personnel: Army, class 3 (authority 1 *a*)

1. Rated command pilots
2. Technical observers
3. Officers of other arms and services detailed by competent authority to duty involving flying.

VI. Functional requirements for class 3 of the Army

Vision without glasses: each eye 20/100

Vision with glasses: each eye 20/20

Refraction: each eye less than + 1.5 or — 1.5 D. spher. or + 0.5 or — 0.5 D. cyl (with cycloplegic)

Field of vision: less than 15 degrees of contraction in any meridian

Color vision: completion of Ishihara or Stilling and Holmgren tests

Depth perception: not required, except for command pilots (at 6 meters, 35 mm. limit)

Muscles, extrinsic (authority 1 *b*)

Heterotropia: none

Esophoria: less than 12 D.

Exophoria: less than 7 D.

Hyperphoria: less than 2 D.

Red lens test for diplopia: test omitted except for command pilots (no diplopia within 27.3 cm. permitted)

Power of divergence: test omitted

Angle of convergence: test omitted

Accommodation: glasses for near vision required while flying and ability to read test at 50 cm.

SECTION 2.—The disqualifying conditions and diseases for all classes or groups of the Army and the Navy Air Corps are as follows (authority 1 *b*, section 3, paragraph 21):

1. Any defect of a permanent nature materially interfering with the normal functions of the eye.

2. The disqualifying conditions and diseases enumerated in the tabulations for the Army and the Navy.

SECTION 3.—The authorities for the ophthalmic requirements of the Air Corps are as follows:

1. Army

Medical Department: Standards of Physical Examination for Flying, Army Regulations 40-110, (*a*) sect. 1, par. 3; (*b*) sect. 3, par. 16-27, April 1, 1940, United States War Department.

2. Navy

(*a*) Physical Examinations for the Medical Department of the United States Navy, Reprint of Chapter 11, Manual of the Medical Department, 1938, sect. 23, par. 1549-1561.

(*b*) Manual of Medical Department United States Navy, Appendix D, Manual of the Medical Department, Bureau Circular Letter R, July 1, 1940, par. 1539a, 1549-1561.

MISCELLANEOUS INFORMATION

Attention should be called to the fact that in the United States Navy vision is to be expressed as a fraction, of which the numerator shall be the distance at which Snellen's 20 foot test letters can be determined and the denominator is 20 when vision is defective or normal. When vision is better than normal, the denominator shall be 15 or 10 as the case may be. Thus 20/20 indicates normal vision, 15/20 less than normal and 20/15 or 20/10 better than normal.

The importance of verifying vision in the military service must not be underestimated. A simple method is to use any 20 foot (610 cm.) letter for all persons with subnormal vision, having the examinee approach until he can call an unknown letter. For further verification use slightly larger or smaller letters. Thus a person with a vision of 20/40 in one eye would have to come to 10 feet (305 cm.) to distinguish a 20 foot letter. He would also see the 30 foot (914 cm.) letter at approximately 15 feet (457 cm.) and the 15 foot letter at approximately 8 feet (244 cm.). Obviously, the test letter or figure should be jet black on a clean white background and have a luminosity of approximately 10 to 15 foot candles. The examinee should have the untested eye completely occluded without pressure. Peeping at the test letters through the fingers which are supposed to cover the untested eye and memorizing test chart letters are among the tricks with which ophthalmic examiners should familiarize themselves.

During the past year, as a member of an advisory Selective Service board, I have found pure ophthalmic malingery to be practiced by far fewer than 1 per cent but have found exaggeration of visual defects practiced by approximately 2 per cent of examinees.

The following tests for malingery and exaggeration are described in "Standards of Physical Examination During Mobilization, Mobilization Regulations 1-9," section 4, paragraphs 19 to 20: (1) stereoscope, (2) bar, (3) mirror, (4) prism, (5) colored lens and (6) trial glass tests and (7) examination of the pupils.

The technics used in testing visual acuity are mentioned in the following authorities:

1. Army

   (*a*) Medical Department: Standards of Miscellaneous Physical Examination, Army Regulations 40-100, United States War Department, Sept. 10, 1940, par. 16-27.

   (*b*) Medical Department: Standards of Physical Examination for Flying, Army Regulations 40-110, United States War Department, April 1, 1940.

2. Navy

   Physical Examinations for the Medical Department of the United States Navy, Reprint of Chapter 11, Manual of the Medical Department, 1938.

Color vision in the Army is tested with the Ishihara test, Stilling plates and Holmgren skeins. In the Navy the Stilling plates are employed, with use of the Edridge-Green lamp as a supplementary test. The Stilling plates as used by the Navy should apparently be adopted by the Army and adapted to the specific needs of the different departments.

The taking of visual fields is required only when indicated by the results obtained with finger and fixation tests.

Temporary night blindness should apparently be considered as a separate entity from the permanent type.

Although waivers are apparently justified in limited instances, their promiscuous use works an unfair hardship on those who are expected to comply with military regulations. Obviously, their limit cannot be made public.

"Conditions and diseases not mentioned in the regulations previously mentioned and which may cause disqualification of the selectee are to be looked for and recorded by the examining physician" ("Selective Service Regulations," United States War Department, vol. 6, par. 606).

Diseases of a selectee reportable by law must be reported to the civil authorities through the proper channels ("Selective Service Regulations," United States War Department, 1940, vol. 6, par. 614-615).

The visual tests involved in reexaminations are not given because of their limited usefulness to the large majority of military ophthalmic examiners. They are included in the following authorities:

1. Medical Department: Standards of Miscellaneous Physical Examination, Army Regulations 40-100, United States War Department, Sept. 10, 1940, pp. 1-19.
2. Circular 117, United States War Department, Oct. 18, 1940.
3. Medical Department: Standards of Physical Examination for Flying, Army Regulations 40-110, United States War Department, April 1, 1940.
4. Physical Examinations for the Medical Department of the United States Army, Manual of the Medical Department, 1938.

CONCLUSION

In conclusion: I will appreciate reports of inaccuracies and ambiguities observed by readers.

This compilation was made possible by the Surgeon Generals of the Army and the Navy. The following persons were of assistance: Dr. E. Schmerl; Colonel Robert E. Strong, Medical Corps, United States Army; Captain T. W. Reed, Medical Corps, United States Navy; Lieutenant Commander J. E. Fulghum, Medical Corps, United States Naval Reserve, and Mrs. E. C. Ferrel.

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News and Notes

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

Indiana Academy of Ophthalmology and Otolaryngology.—The annual meeting, held at the Claypool Hotel, Indianapolis, April 1, was called to order by President Dr. Noel S. McBride, of Terre Haute, and the following program was presented: "Ophthalmology: Past, Present and Future," Dr. Noel S. McBride, Terre Haute; "Two Unusual Cases of Mastoiditis," Dr. Kenneth L. Craft, Indianapolis; "Ophthalmoplegic Migraine," Dr. H. Brooks Smith, Bluffton; "Osteoma of the Nasal Sinuses: Case Reports," Dr. Hugh A. Kuhn, Hammond; "Perimetric Studies in Some of the Toxic Amblyopias," Dr. C. E. Savery, South Bend; "The Sulfa Drugs Used Locally in Otolaryngology," Dr. S. S. Aronson, Indianapolis; "Problems in Cataract Surgery," Dr. D. H. Row, Indianapolis; "Injuries and Deformities of the Nose," Dr. Claire LeRoy Straith, Detroit; "Acute Mastoiditis with Intracranial Complications," Dr. David Jones, Indianapolis.

After the annual dinner, Dr. Straith presented colored motion pictures dealing with plastic operations on the head and face.

Pacific Coast Oto-Ophthalmological Society.—The thirtieth annual session was held at the Benson Hotel, Portland, Ore., May 11 to 13 under the presidency of Dr. Ralph Fenton, Portland, whose address was entitled "War and Peace." Among the speakers were the following: Dr. Gordon B. New, Rochester, Minn., "Immediate and Later Care of Facial Injuries"; Dr. Augustus G. Pohlman, Los Angeles, "Hearing Aids"; Dr. Phillips Thygeson, New York, "The Sulfanilamide Group," and Dr. John E. Raaf, Portland, "Perimetric Diagnosis of Intracranial Lesions."

Ohio State Medical Association.—At the recent annual meeting the following officers of the Eye, Ear, Nose and Throat section were elected: president, Dr. William H. Evans, Youngstown, and secretary, Dr. Harry C. Rosenberger, Cleveland.

Cleveland Otolaryngological Society.—At the recent annual meeting Dr. Horace E. Mitchell was elected president and Dr. J. W. McCall secretary.

GENERAL

Additional Care for the Blind in Pennsylvania.—Plans are under way to launch a new, expanded program providing additional care for blind and visually defective persons in Pennsylvania. The program was authorized by the last general assembly. The state council for the blind will administer the plan, which will be far more comprehensive than the state's past activities for blind and visually defective persons. Regional supervisors will be assigned to various sections of the state to carry on the work in defined areas, according to the *Pennsylvania Medical Journal.*

Grady Hospital, Atlanta, Ga.—The Eye Pathological Laboratory was recently opened. The unit occupies space in the Gray Clinic of the hospital and will be available to all ophthalmologists. It is the gift of Mr. L. F. Montgomery, Atlanta, an alumnus of Emory University. Dr. F. Phinizy Calhoun Jr. and Dr. William T. Edwards are in charge of the laboratory. According to the *Bulletin* of the Fulton County Medical Society the laboratory is the only one of its type in the Southeast and is one of about nine of its kind in the country.

PERSONAL

Dr. William E. Bruner Honored.—Dr. William E. Bruner, professor emeritus of ophthalmology, Western Reserve University School of Medicine, Cleveland, was honored during a recent meeting of the Cleveland Medical Library Association. His portrait was presented to the association, and an alcove in the library was named for him. The room was made possible by contributions from the Cleveland Ophthalmological Club. Dr. Bruner is a charter member of the association and has served it as president, secretary, treasurer, chairman of the finance committee and member of the board of trustees.

Dr. Goldsmith Awarded Prize.—At the 1942 annual meeting of the Medical Society of the State of New York Dr. Jacob Goldsmith was awarded the Lucien Howe prize for his essay entitled "Original Studies on the Internal Dynamics of the Intracapsular Cataract Extraction."

Obituaries

HENRY ROBERTSON SKEEL, M.D.
1885-1942

Death claimed Henry Robertson Skeel on March 22 at the untimely age of 56. Born on Oct. 4, 1885 in Mott Haven, N. Y., in the house where his mother also was born, a house built in 1851 by his grandfather Robertson as a country residence, Dr. Skeel was the son of Dr. Frank D. Skeel and Mary Robertson Skeel. (His father was for many years attending ophthalmologist to the New York Eye and Ear Infirmary and is especially remembered for his studies in perimetry.)

After preliminary schooling in Morris High School, Dr. H. R. Skeel went to Wesleyan University and received the Bachelor of Arts degree in 1909; he was graduated in medicine from Columbia University College of Physicians and Surgeons in 1913. He had a general internship at the Lenox Hill Hospital and an ophthalmologic residency at the Manhattan Eye, Ear, and Throat Hospital, and then entered practice in 1916 with his distinguished father, the partnership lasting until the latter's death in 1923.

For a time Dr. Skeel was affiliated with the Knapp Memorial Eye Hospital, but his principal and life-long hospital connection was with the Manhattan Eye, Ear, and Throat Hospital, where, in the service of the late Dr. Edgar S. Thomson, he rose through the successive grades of clinical assistant, assistant surgeon, junior surgeon and surgeon, and for the eight years preceding his death he had occupied the position of surgeon director. Essentially a clinician, he was an able ophthalmic surgeon and a truly gifted refractionist. Since he was born in the Bronx and lived there continuously for almost forty years, it was fitting that he was consulting ophthalmologist to the Bronx Eye and Ear Infirmary.

In 1917 he was appointed to the Advisory Council of Physicians of the New York State Commission for the Blind, which maintained an ophthalmic clinic at Sing Sing prison, and for a period of over ten years he was ophthalmologist to the penitentiary, where he trained some of the inmates to assist him in the niceties of ophthalmic surgery. Many of these boys from the "Big House" after their release were his devoted and loyal admirers, and he was unaffectedly proud of his contribution to their rehabilitation.

In World War I Dr. Skeel was an early volunteer, seeing service overseas as a captain in the late Colonel Wilmer's detachment in the

Third Aviation Instruction Center. The men with whom he was associated in this experience were his close friends through life.

Death came to Dr. Skeel as the result of a coronary closure suffered two weeks earlier. During the preceding two years, following his first attack, he had been free from symptoms and had been able to indulge in limited activity and professional practice. Interment was in the family plot at Bedford, N. Y.

Dr. Skeel was married in 1924 to Helen Seybolt of Oneonta, N. Y., who survives him.

He was a member of the New York county and New York state medical societies, the American Medical Association, the New York Academy of Medicine, the New York Ophthalmological Society and the Chi Psi fraternity.

Descended on his father's side from a long line of New England forebears and through his mother from the Robertson clan, Dr. Skeel was passionately devoted to the Anglo-Saxon tradition. His character exemplified the traits of his ancestors—loyalty, dependability, tidiness, thrift, hospitality, ingenuity, determination. He was never happier than when in his country home in Bedford, N. Y.—either entertaining friends or working quietly in his well equipped workshop. His hobbies were photography, clocks, old rugs and furniture. He loved travel, good music, a good book, a good story, a good friend. He was somewhat shy, and his intimates were few, but they indeed were privileged.

GUERNSEY FREY.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Anatomy and Embryology

ANATOMY OF THE CHOROID, CILIARY NERVES AND INSERTION OF THE OBLIQUE MUSCLES ON THE MACULA. E. P. FORTIN, Arch. de oftal. de Buenos Aires **15:** 124 (March) 1940.

This is a histologic study, illustrated with several photomicrographs, in which the author's views are somewhat at variance with those usually held.

He considers Brücke's view of the ciliary muscle as a tensor of the choroid in accordance with modern investigations. Its internal bundle is involved in accommodation. Its two principal insertions are in the form of a tendinous ring on the internal lip of Schlemm's canal and on the walls of the choroidal veins. There is no adhesion of the choroid to the internal surface of the sclera, as is often erroneously maintained. The tail of the muscle twists around the globe as far back as the optic nerve. It consists of conglomerate bundles with an intervening liquid. The author denies the existence of any connective tissue stroma. Each bundle terminates in a tendinous lamina. Those attached to the veins are shorter and those attached to the lamina fusca longer.

The choroidal veins form a venous lake which surrounds Jacob's membrane, from which it is separated by the pigment layer, the venous channels having extremely thin walls.

The pigment layer is separated from the choroidal veins by Brücke's membrane, which according to modern authors is separable into two layers which react differently to coloring agents. The author calls attention to the similarity of Brücke's membrane to the limitans externa et interna.

The lamina fusca does not form a continuous layer, being perforated at multiple points and containing numerous chromatophores.

With Lauber and Klein, the author finds muscle bundles in the neighborhood of the macula.

He refers to the tapetum in felines; it does not exist in man.

Numerous ciliary nerves surround the optic nerve entrance; they penetrate the sclera obliquely and have a relatively wide section. The myelin covering is not so apparent in the neighborhood of the iris.

C. E. FINLAY.

Bacteriology and Serology

ALLERGY STUDIES ON TUBERCULOUS EYES. B. BOROS, Arch. f. Ophth. **142:** 356, 1940.

The author applies to ocular tuberculosis Gröer's concept of tuberculous allergy, according to which the intensity of local reactions to the application of allergens depends on the ratio of reactivity to susceptibility. The relative share of each of these two factors can be

determined by the simultaneous application at different places of two different concentrations of the stimulus, that is of tuberculin. If reactivity and susceptibility are in a state of equilibrium (called homodynamic allergy by Gröer) the product of the average diameter of the cutaneous reaction (read after twenty-four hours) times the negative logarithm of the tuberculin concentration is constant. If R_1 and R_2 were the average diameters of the cutaneous reactions produced by the concentrations of C_1 and C_2 respectively, of tuberculin in a case of homodynamic allergy the proportion would hold:

$$R_1/R_2 = -\log C_2/-\log C_1, \text{ or } \frac{R_1 \times -\log C_1}{R_2 \times -\log C_2} = 1$$

If the latter ratio in a given case is greater than 1, that is if the increase in cutaneous reaction produced by a certain increase in tuberculin concentration is greater than in homodynamic allergy, Gröer spoke of pleoergic, and in the opposite case of pleoesthetic, allergy. The interpretation of tuberculin tests in the light of Gröer's concept gives valuable clues with regard to the activity, healing tendency and probable future of tuberculous diseases occurring in children. In adults the allergic state of the skin may be different from that of other organs. (The experimental work of A. C. Woods and associates on regional differences in sensitivity to tuberculin is not mentioned.)

The three states of allergy were found to occur in patients with ocular tuberculous diseases as shown in the accompanying table.

States of Allergy in Ocular Tuberculous Diseases

	No. of Cases		
	Pleo-ergic	Homo-dynamic	Pleo-esthetic
Phlyctenular keratitis	5	10	5
Iridocyclitis	8	4	1
Choroiditis	7	5	1
Sclerokeratitis	4	2	2
Retinal periphlebitis	2	2	1
Orbital periostitis	..	1	..

In the individual patient the allergic state was found not to vary with the different phases (activity, inactivity, progression, regression) of the ocular disease. A chemotherapeutic agent of the name rubrophen (trimethyldioxyoxytritan) seemed to modify it, and the alteration seemed to have a beneficial effect on the ocular disease. "In the pleoesthetic state tuberculin must not be used." P. C. KRONFELD.

Biochemistry

CONTENT OF ASCORBIC ACID (VITAMIN C) IN AQUEOUS, LENS AND BLOOD OF CATARACTOUS AND NONCATARACTOUS PERSONS. P. GAPEEV, Vestnik. oftal. **18:** 154, 1941.

In order to establish the relation between the content of vitamin C in the body and the formation of senile cataract, Gapeev examined 48 cataractous patients and 8 noncataractous patients. In 29 cases the

vitamin C content of the aqueous, the lens and the blood was determined. In 16 the lens in the capsule and in 25 the lens without the capsule was examined. The method of determining the vitamin C content was Tillman's for the aqueous and Farmer's for the blood.

A decrease in the vitamin C content of the aqueous, the lens and the blood in cataractous patients as compared with patients with normal eyes was found by Gapeev as follows:

1. In the aqueous and the lens of the normal eye the vitamin C content was from 7.7 to 15.8 mg. per hundred cubic centimeters.

2. The vitamin C content of the acqueous and the lens of the cataractous eyes was from 2.8 to 7.4 mg. per hundred cubic centimeters.

3. The vitamin C content of the blood was from 0.3 to 1.2 mg. per hundred cubic centimeters in patients with normal eyes while it was only from 0.08 to 0.46 mg. in the cataractous patients.

4. The large amount of vitamin C in the aqueous and the lens as compared with the low amount in the blood of cataractous patients does not indicate a relation between the two.

Three tables illustrate the article, and a detailed review of the literature is given.

O. SITCHEVSKA.

Conjunctiva

CYST OF CONJUNCTIVA AFTER ENUCLEATION. M. KRASNOV, Vestnik oftal. **18:** 199, 1941.

In a man aged 23 an eye injured in childhood was enucleated and fat implanted. A conjunctival cyst formed two and a half years later and attained the size of a walnut, so that a prosthesis could not be retained. An electrocoagulation was done and repeated in six weeks, after which the cyst was reduced to a small hard nodule.

Krasnov believes that this serous cyst might have formed because folds of the conjunctiva turned in during the sewing up of the conjunctiva.

O. SITCHEVSKA.

TUBERCULOSIS OF THE CONJUNCTIVA. N. BLUMENFELD, Vestnik oftal. **18:** 203, 1941.

Three patients with tuberculosis of the conjunctiva have been seen since 1935 in the ophthalmic clinic of the Crimean Medical Institute. They were 10 years, 2 years and 19 months old, respectively. In 2 the process in the conjunctiva was primary, while in the third it was secondary to tuberculosis of the lungs. The inoculation of guinea pigs intraperitoneally and into the anterior chamber gave a positive reaction in all cases. Ulceration of the conjunctiva of the upper lid with papillomatous granulation and swelling of the preauricular and submaxillary glands was present in all cases. The histopathologic examination showed a tuberculous ulcer with a caseous necrotic center and with epithelioid and giant cells. Surgical removal of the ulcer with cauterization of the wound was followed by cicatrization. Tuberculin therapy and general hygienic measures were also employed.

O. SITCHEVSKA.

PARINAUD'S SYNDROME AND TUBERCULOSIS OF THE CONJUNCTIVA. N. OCHAPOWSKAYA, Vestnik oftal. **18:** 278, 1941.

Ochapowskaya discusses the etiology and clinical picture of Parinaud's syndrome and reports a case in which Parinaud's conjunctivitis proved to be true tuberculosis of the conjunctiva.

A girl aged 15 had a swelling of the left upper lid and of the left preauricular gland for six months. It was diagnosed by a competent ophthalmologist as Parinaud's conjunctivitis. The conjunctiva of the upper lid was infiltrated, and there were vegetations of various sizes, with ulceration. The left preauricular gland was swollen and had two fistulas. Bacteriologic examination of the conjunctival secretion gave negative results. A biopsy of the conjunctiva showed under the microscope typical giant cells, lymphoid cells and epithelioid cells with moderate necrosis.

A second patient was a woman 20 years old in whom the conjunctiva of the right eye was affected and the clinical picture was characteristic of tuberculosis. Since the microscopic examination did not show any giant or epithelioid cells, a diagnosis of Parinaud's conjunctivitis of undetermined causation was made.

The conclusions were as follows:

1. Parinaud's conjunctivitis represents a reaction of the conjunctiva grossly homogenous to but microscopically different from the reaction to various etiologic, frequently undetermined, factors.

2. The further study of Parinaud's syndrome produced more confusion. Ochapowskaya believes that (*a*) Parinaud's conjunctivitis is not an independent nosologic unit and that (*b*) Parinaud's syndrome can imitate grossly various infections such as tuberculosis, syphilis, tularemia and sporotrichosis.

3. Each case should be individually studied from the etiologic point of view in order that a refinement of the prognosis and the therapy may be achieved.

O. SITCHEVSKA.

Cornea and Sclera

MACROCORNEA AND BUPHTHALMOS: REPORT OF CASES. K. VOM HOFE, Klin. Monatsbl. f. Augenh. **104:** 278 (March) 1940.

The author contends that corneas measuring from 12.5 to 13 mm. or more are abnormally large, that the condition they represent is termed macrocornea but that this term refers in no way to the genesis. His clinical observations convinced him that genetic relations exist between buphthalmos, which is the infantile glaucoma, and macrocornea. Among the material observed were two families in each of which 1 child suffered from buphthalmos whereas most of the other children had large or even abnormally large corneas but no symptoms of a present or past increase of intraocular tension. Similar observations made by the author are published in the present paper. In one family large corneas and buphthalmos were found in several members. One boy had entirely healed infantile glaucoma appearing as macrocornea in one eye and typical buphthalmos in the other eye. In another child and his grandfather inherited megalocornea and cornea globosa, respectively, were observed. The typical

cupola-shaped cornea was present in the child only. Two patients were proof for Peter's contention that in macrocornea the curvature of the cornea may be decreased while the radius is larger than normal. Vom Hofe stresses the finding of an abnormally large cornea in the mother of a child with typical buphthalmos. He opposes the idea that the mother's macrocornea represented buphthalmos arrested at an early stage. The author concludes from this material that genetic relations exist between macrocornea and buphthalmos. The large cornea may predispose to the development of buphthalmos. The corneal radius is irrelevant in this matter. Even if megalocornea globosa represents a separate type of macrocornea, the tendency toward glaucoma remains evident.

K. L. STOLL.

MEGALOCORNEA: EXAMINATION OF A PATIENT OPERATED ON FOR CATARACT AND OF HIS FAMILY; REPORT OF A CASE. R. KLAR, Klin. Monatsbl. f. Augenh. **104:** 286 (March) 1940.

The author reviews the publications on megalocornea, beginning with Hasner's paper of 1858 and including Vails' paper of 1931. Vail devised eighteen operations for cataract, twelve of which were successful. Klar discusses contradictory opinions held by various authors on the terminology and then reports in detail the history of a patient on whom he operated for cataract and that of the patient's family. Five members of the family had megalocornea, or enlarged corneal radiuses. Three generations were involved, and fifteen members were examined.

Discussing the opinions of divers writers, Klar accepts the measurements of Donders for the normal radius of curvature of the cornea: in the vertical meridian 7.7 mm. and in the horizontal meridian 7.8 mm. for men and slightly smaller for women. Measurements of 13 mm. or more justify the diagnosis of megalocornea. The corneal radiuses were "enlarged" in Klar's patients and also in the brother and son, who were afflicted with megalocornea. Apart from these persons, a number of members of the family showed large corneas, although they presented no megalocornea (the mother and the sister and her two children). Although enlarged corneal radiuses are considered a distinct sign of hydrophthalmos, Klar's patients with enlarged corneal radiuses had genuine megalocornea. Two brothers and the son, who was operated on for cataract, had deep anterior chambers but no symptoms indicating past or present intraocular hypertension.

Further observation will show whether the boy will have changes at the posterior surface of the cornea, the iris and the lens such as were found in his father and his uncle. In these 3 patients the diameters of the left cornea were larger than those of the right. It is possible that the gene in this family was strong enough to produce megalocornea notwithstanding the enlarged corneal radius. The lens after intracapsular extraction weighed 0.33 Gm.; it measured 11.25 mm. equatorially and 6.5 mm. sagittally. Postoperatively the distance vision was 5/7, and the patient could read Nieden type 1. He returned to work.

Klar concludes: 1. Genuine megalocornea as a dominant character was observed. 2. The corneal radius may be enlarged in genuine megalocornea. 3. The type and the extension of the corneal opacities failed to

show similarity in brothers with megalocornea. 4. The cataract, in its capsule, of a patient with megalocornea was larger and heavier than any hitherto reported; this fact allows no generalizing conclusions. Further extractions may later make possible a decision on whether or not the lens takes a regular part in the enlargement of the anterior segment of the eyeball in megalocornea.

K. L. STOLL.

SUPPOSED RELATION BETWEEN MACROCORNEA AND HYDROPHTHALMOS AND ITS LACK OF PROOF. B. KAYSER, Klin. Monatsbl. f. Augenh. **106:** 63 (Jan.) 1941.

In the first chapter of his paper Kayser discusses the cases published by K. vom Hofe and R. Klar (*Klin. Monatsbl. f. Augenh.* **104:** 278 and 286, 1940) and the views expressed by these authors. Kayser considers both cases as rare exceptions and an unsuitable basis for general conclusions. He sums up his opinion on the relation between macrocornea and hydrophthalmos as follows: 1. The term macrocornea is a collective term for several primary and secondary forms which must be separated from one another. 2. Only cases of macrocornea in which the radius exceeds 13 mm. may be adduced for critical proof. 3. Hydrophthalmos sanatus is the only form of macrocornea definitely related to hydrophthalmos. 4. Among the other types of macrocornea, primary and secondary, there is one in which clinical observation suggests the existence of a genetic relation with hydrophthalmos; proof, however, has not been established. 5. Vom Hofe's explanation of such a relation is insufficient. A large number of points in contradiction to it are contained in an earlier paper by Kayser (*Klin. Monatsbl. f. Augenh.* **102:** 11, 1939) and the present paper. 6. Megalocornea, a distinctly separate form of macrocornea, has no relation to hydrophthalmos.

K. L. STOLL.

SPORADIC MEGALOCORNEA GLOBOSA: REPORT OF A CASE OF CATARACT EXTRACTION IN MEGALOCORNEA. A MIKLÓS, Klin. Monatsbl. f. Augenh. **106:** 69 (Jan.) 1941.

Megalocornea, in Miklós' opinion, is a healed form of hydrophthalmos. It manifests itself by ruptures in Descemet's membrane and by other glaucomatous changes. A case is reported of bilateral nonfamilial megalocornea, the so-called sporadic type of megalocornea globosa. The patient, a farmer aged 42, was struck in his left eye by the tail of a horse. The ensuing cataract was successfully extracted. The entrance of the orbit measured 39 mm. in the horizontal meridian and 30 mm. in the vertical. Refraction was 40 by 40 D.; the radius of the corneal curvature was 8.5 mm.; the horizontal diameter of the cornea measured 18 mm. and the vertical diameter 17 mm. The luxated cataract was removed with Weber's loop. Other details on the operation and the study are given, including the results of slit lamp examination (observations of Bowman's lymph tubules in the cornea). The mechanism of luxation of the lens or of cataract, respectively, in megalocornea, resulting from the condition of the zonula, is discussed, and the views of several groups of authors are included.

The presence of Bowman's lymph tubules was considered proof of the existence of formed lymph clefts in the human eye, the existence of which has been disputed by several authors. Miklós does not consider megalocornea and hydrophthalmos as identical diseases. The characteristic symptoms of juvenile glaucoma are absent in megalocornea, and the latter differs decidedly from congenital hydrophthalmos.

During extraction of the luxated cataract in this case it was impossible to safeguard the wound by a conjunctival flap, because the enlarged and prominent cornea caved in after release of the tension; partial securing was obtained by adaptation of the edges of the wound through corneal sutures. Iridectomy is recommended in anticipation of complications during operation. Extraction in the capsule may be attempted, but use of Weber's loop is preferable.

K. L. STOLL.

General Diseases

SIGNIFICANCE OF DIFFERENTIAL BLOOD COUNT IN DIAGNOSIS AND TREATMENT OF OCULAR TUBERCULOSIS. H. SCHMELZER, Arch. f. Ophth. **142:** 338, 1940.

This paper represents an abstract of a monograph by the same author entitled "Differential Blood Count and Ocular Tuberculosis" (Leipzig, Johann Ambrosius Barth, 1939). Tuberculosis may be assumed to be the probable cause of a chronic or recurrent ocular inflammation if other causes have been ruled out and definite signs of a tuberculous infection are present in the patient or in persons with whom he has been in intimate contact. A marked reaction to the intradermal injection of tuberculin makes the diagnosis more probable. Focal reactions to the diagnostic tuberculin test should be avoided. "The least toxic tuberculin should be used." Schmelzer uses Toenniessen's tebeprotin (human tubercle bacillus protein) exclusively. He believes that "tuberculin in the hands of an experienced physician represents an extremely effective and not at all harmful means of therapy." Most of the recurrences of tuberculous uveitis are tuberculoallergic reactions of the eye, each flare-up being associated with increased sensitivity to tuberculin. The aim should be to eliminate hypersensitivity by careful desensitization. To carry out this treatment properly accurate knowledge of the patient's state of immunity and sensitivity is essential. The author recommends a new gage, namely the differential white cell count. He first determines the variations in the count which take place after the diagnostic injection of tuberculin (usually 0.1 mg. of tebeprotin given subcutaneously). There are several characteristic types of reaction:

Type 1 is a marked relative increase of the neutrophils associated with a drop in the number of lymphocytes. In patients with this type of reaction tuberculin causes severe systemic and local reactions (extreme sensitivity, unfavorable state of immunity).

Type 2 is a marked relative increase of the lymphocytes with a corresponding drop of the neutrophils. This reaction indicates moderate but definite allergy to tuberculin (moderate sensitivity, favorable state of immunity).

Type 3, no change in the differential count, is usually encountered in patients who give no cutaneous or general reaction to tuberculin (insensitivity).

A relative increase of the monocytes is indicative of a tendency toward hypersensitivity. An increase in the eosinophils has the same meaning as a reaction of type 1. For patients with this type of reaction the author does not advise tuberculin therapy. If tuberculin is used at all the doses should be extremely small and the intervals long, and the differential count should be watched closely.

Tuberculin therapy is definitely indicated for patients giving a reaction of type 2. But with them, too, differential counts taken once or twice a month give valuable information with regard to the changes of sensitivity and immunity under the influence of the specific therapy.

The author does not state clearly his own concept with regard to the relation between immunity to tuberculosis and sensitivity to tuberculin.

P. C. KRONFELD.

Glaucoma

PILOCARPINE TEST OF ADAPTATION IN EARLY DIAGNOSIS OF PRODROMAL GLAUCOMA. A. DASHEVSKIY, Vestnik oftal. **18:** 241, 1941.

On the basis of his clinical material and reports in the literature Dashevskiy states that there is a definite decrease of adaptation in glaucoma (in nearly 100 per cent of cases) and also of sensitivity to light (in 80 to 90 per cent) in prodromal glaucoma. However, no definite diagnosis of prodromal glaucoma can be made on the basis of the subjective symptoms and lowered dark adaptation alone. Dashevskiy offers a new, sensitive functional test, namely the study of dark adaptation as influenced by pilocarpine. The various stages of the study are presented as follows:

1. The influence of the size of the pupil on the adaptation. Thirty-five eyes (18 subjects) were studied with stenopaic holes 2, 4, 5 and 6 mm. in diameter. The final size for sensitivity to light was determined several times in various series of the experiment. In one of the series the study was made with the pupil dilated in the dark (without measuring the size of the pupil). The conclusion drawn from this stage of the experiment was that it is important to use the stenopaic hole and that it is possible to use the functional tests in clinical practice.

2. The diagnostic pilocarpine test of adaptation in glaucoma. The following method was used:

The pilocarpine drops were discontinued for a day. After disadaptation to daylight, the patient was kept in a dark room for forty-five to fifty minutes and then the sensitivity to light determined for each eye separately, the size of the pupil not being measured. The 2 mm. stenopaic hole was then used and the sensitivity to light measured again. It showed a decrease. One drop of 2 per cent pilocarpine solution was then instilled, and the procedure was repeated; i. e., the sensitivity to light was measured again with an artificial-sized pupil (2 mm.) after pilocarpinization.

It was proved that in normal eyes the pilocarpine test did not influence the sensitivity to light, while in glaucomatous eyes the sensitivity was higher after the use of the drug.

3. Clinical observations.

During the years 1936 to 1938 250 tests were done. Careful perimetric, campimetric and dark adaptation tests with Dashevskiy's adaptometer were also done; 152 tests were done on eyes with suspected prodromal glaucoma and 98 on eyes with definite glaucoma (90 eyes). In most of the cases of glaucoma the pilocarpine test of adaptation gave a positive reaction and only the light threshold varied according to the advancement of the disease. It gave negative results in 8 cases of marked glaucoma when the atrophic changes set in, indicating that the use of pilocarpine was of no value and that surgical intervention would be preferred.

Of eyes with suspected prodromal glaucoma the pilocarpine test gave a positive result in 79 and a negative one in 73.

The tests on 152 eyes suspected of being in the prodromal period of glaucoma showed limitation of the visual fields (43 per cent), inversion of the field for blue, a decrease of the dark adaptation (54 per cent), enlargement of the blindspot and angioscotomas (78 per cent). The pilocarpine test was decisive in the diagnosis of glaucoma, as it was positive in 79 cases in which the functional defects mentioned were present. The test is similar to the angioscotometric test, but it has the advantage that it can be done on patients with poor vision or with low intelligence and that the fixation is not as prolonged.

O. SITCHEVSKA.

Methods of Examination

ROENTGEN EXAMINATION IN OPHTHALMOLOGY. H. ROCHA, Ophthalmos **1:** 62, 1939.

The author discusses the value of roentgenologic examination of the lacrimal passages and of intraocular calcifications. Iodized poppy-seed oil and iodized sesame oil were used as opaque mediums for visualization of the lacrimal passages. A roentgenogram of a mucocele in the lacrimal passages is useful from the point of view of the operative procedure. Permeability after dacryocystostomy can also be investigated by means of roentgenograms. The differential roentgenologic diagnosis of the various types of intraocular calcification (choroid, retina and lens) is discussed. In cases in which the tonometric reading is low when the digital tension feels high, intraocular calcification must be suspected.

The article is illustrated.

P. MONTALVÁN.

LOCALIZATION, AFTER COMBERG'S METHOD, OF INTRAOCULAR FOREIGN BODIES BY ROENTGENOGRAM WITH PATIENT RECUMBENT. F. K. LEYDHECKER, Klin. Monatsbl. f. Augenh. **104:** 308 (March) 1940.

The author describes in detail his manner of taking roentgenograms for the localization of intraocular foreign bodies after Comberg's method. His modification is especially adapted for patients who cannot be moved freely because of injuries other than ocular lesions. Foreign bodies in

the vitreous may be localized in the same position, which can be used during an eventual operation. The lead markers of Comberg's prosthesis are less readily displaced with the patient in this position than with him in the upright position or with the head in a lateral position. Stereograms can be taken. An easily adaptable scale after Maddox with movable lamp for use in the x-ray room is described. K. L. STOLL.

Neurology

MENINGIOMA OF THE FRONTO-ORBITAL REGION. J. SANTA CECELIA and P. ELEJALDE, Ophthalmos **1:** 9, 1939.

A case of meningioma of the fronto-orbital region in an 18 year old girl is presented. The tumor involved the frontal region, the base of the nose and the lower lids and was accompanied with exophthalmos and advanced optic nerve atrophy. Roentgen examination revealed destruction of bone in the areas involved. The patient died of intercurrent pneumococcic meningitis. Necropsy disclosed considerable destruction of the frontal and other bones comprising the upper part of the face and of the anterior base of the skull by the tumor mass, which was pasty in consistency, with a harder central core. From the histologic standpoint, the greater part of the tumor consisted of endothelial-like cells somewhat elongated and arranged irregularly in certain areas, while in others they showed a tendency to tubular formations. A diagnosis of meningioma omniformis and acute purulent meningitis was made.

The authors discuss at length the different classifications of meningeal tumors and adopt the recent one proposed by Globus.

The article is illustrated. P. MONTALVÁN.

Ocular Muscles

MONOCULAR DIPLOPIA OCCURRING IN CASES OF SQUINT. E. E. CASS, Brit. J. Ophth. **25:** 565 (Dec.) 1941.

Cass reviews the literature of monocular squint in reference to the explanation of the phenomenon of monocular diplopia.

He examined 70 patients with squint with abnormal correspondence and found that 33 obtained monocular diplopia, 51.2 per cent on stimulation of the false corresponding point, 33.3 per cent on stimulation of both the false corresponding point and the macula and 15.2 per cent on stimulation of the macula only.

The squint of 78 per cent was not comitant; that is to say, these patients showed a definite lesion, either paresis or overaction of a muscle. At operation 7.7 per cent were found to have abnormal muscle insertion. In 144 per cent of the cases in which monocular diplopia was obtained the squint was associated with nystagmus.

Some observations associated with the second image in monocular diplopia were:

"(1) Generally in the beginning it is much dimmer than the first image.

"(2) Its colours are less well defined.

"(3) In the beginning, it is very vague and disappears easily.

"(4) It is difficult for the patient to orientate its position in space.

"(5) On prolonged stimulation, one or other image will disappear but if the congenital space value is the stronger, this image will remain.

"(6) On asking the patient to fix either image caused by the stimulation of the eccentric point corresponding to the macula of the other eye, the eye will turn to take up fixation with the macula and the non-fixated image will disappear.

"(7) On telling the child to fix either image excited by stimulation of the macula, there will be no movement of the eye or there will be a slight flicker and the eye later returns to its original position and the non-fixated image will disappear."

This article is illustrated.

W. ZENTMAYER.

ETIOPATHOGENESIS, ORTHOPTIC TREATMENT AND VISUAL REEDUCATION IN FUNCTIONAL STRABISMUS. J. SVERDLICK, Arch. de oftal. de Buenos Aires **14:** 955 (Nov.) 1939.

After reference to the fact that attention was first called to the functional character of strabismus by Celsus, Galen and D'Egina (who used spectacles with a central hole before each eye), Sverdlick reviews the different theories upholding a muscular origin (Buffon, Tenon, Withe, Wenzel, Stromeyer, Dieffenbach, Schweigger, von Graefe, Giraud-Teulon and others), which, with Stellwag, Carrion and Grut he considers unacceptable except in a few cases of congenital strabismus. He next takes up the work of Donders, Javal, Worth, Duane and Bielschowsky and of the Argentines Lagleyze, Argañaraz, Malbrán and Adrogué.

He reviews the history of orthoptic treatment in France and England and details the procedure he follows, which can be condensed into (1) preorthoptic treatment (determination of refraction, treatment of amblyopia and general treatment), (2) preoperative orthoptic treatment (overcoming of image suppression, development of simultaneous macular perception and initial fusion exercises), (3) operation (when necessary) and (4) postoperative orthoptic treatment (completion of development of fusion stereovision and increase of range of fusion and duction).

C. E. FINLAY.

Operations

KERATOPLASTY. R. CASTROVIEJO, Am. J. Ophth. **24:** 139 (Feb.) 1941.

Castroviejo describes a method of circular partial penetrating keratoplasty and discusses various technical phases of keratoplasty. He concludes that keratoplasty is feasible and practicable and that an individual technic is probably preferable but that his method of the square corneal graft incorporates more advantages and less disadvantages.

W. S. REESE.

THE REPAIR OF LACERATED EYES. R. L. REA, Brit. M. J. **1:** 555 (April 12) 1941.

The author describes the well known Kuhnt operation for extensive cuts of the cornea. In the operation pressure on the eyeball should

naturally be avoided. A conjunctival ribbon flap is dissected free from the upper corneal margin. This is brought down over the cornea and laid over the length of the corneal wound. At each side the ribbon is held in place by a conjunctival suture. When the edges of the corneal wound are not in apposition or are not sharply linear an additional suture passing through the edges of the corneal wound and coming out through the conjunctival flap may be required. For this the suture material is a 12 inch (30 cm.) piece of silk threaded at each end with a fine cutting needle such as that used for corneoscleral suturing during cataract operations. If there is any protruding iris it should be cut away. To avoid pressure on the eyeball, Arruga's speculum should be used.

ARNOLD KNAPP.

Orbit, Eyeball and Accessory Sinuses

TUBERCULOUS PANOPHTHALMITIS. N. PASTERNACK, Vestnik oftal. **18:** 31, 1941.

This is the twelfth case of tuberculous panophthalmitis reported in the world literature. A man aged 58 had chronic panophthalmitis due to generalized tuberculosis. At the preequatorial region there was a perforation of the sclera from which pus was draining. The patient refused an enucleation, and a microscopic examination of the eye was done only after his death. No phthisis bulbi was observed, as in cases of panophthalmitis of usual causation, but considerable necrosis and destruction of the eyeball were present. The histopathologic data are reported in detail. No definite indications as to the localization of the primary metastatsis could be found.

O. SITCHEVSKA.

Retina and Optic Nerve

THE SURGICAL TREATMENT OF SYPHILITIC OPTIC ATROPHY DUE TO CHIASMAL ARACHNOIDITIS. L. HAUSMAN, Am. J. Ophth. **24:** 119 (Feb.) 1941.

Hausman suggests a broader view of the pathogenesis of optic nerve atrophy, emphasizing that it may be due to adhesions. He thinks that this etiologic agent is indicated by heteronymous field defects, by multiple cranial nerve lesions adjacent to the optic nerve or by the existence of primary optic nerve atrophy and syphilis as the only signs present. He reports 3 cases in which operation was performed and the optic nerve head freed of adhesions.

W. S. REESE.

CENTRAL RETINITIS IN A GIRL AGED 18 YEARS. RECOVERY. R. FORD, Brit. J. Ophth. **25:** 521 (Nov.) 1941.

The author refers to a previously reported case of recurring foci of choroiditis of undetermined causation in which the vision was greatly improved and further attacks checked by performance of a submucous resection on purely empiric grounds.

In a second case, exudative choroiditis in a girl 18 years of age whose clinical, laboratory and roentgen examinations gave negative results was rapidly improved by the use of peroxide packs in the nasal chambers. Inhalations of compound tincture of benzoin were also administered, and powdered Barbados aloe was given daily. W. ZENTMAYER.

RETINITIS PIGMENTOSA WITH MACULAR DYSTROPHY: REPORT OF A FAMILIAL GROUP. A. SORSBY, Brit. J. Ophth. **25:** 524 (Nov.) 1941.

Sorsby previously reported a case of pigmentary degeneration of the retina with macular dystrophy. In this particular case no hereditary or familial incidence could be established; so there was some lack of validity in drawing on the case for an argument in favor of clearly defined familial and hereditary lesions. The present note supplies the necessary validity, as it concerns a familial group showing the association of the two lesions. Two of the four sons and one of the two daughters were affected. The father was a cousin of the maternal grandfather.

Ophthalmoscopically the two parents showed essentially the same picture. Typical bone-corpuscle pigment was distributed rather unevenly over the different sectors of the fundi, which also showed gross pigmentation here and there. The disks and retinal arteries were characteristic of retinitis pigmentosa, and there was considerable unmasking of the choroidal circulation. The macular lesions were of the dystrophic type.

This group may be taken as lending support to the view that macular dystrophy cannot be put in sharp antithesis to generalized retinal dystrophy, of which retinitis pigmentosa is the best known type. The various clinical types of retinal dystrophy are not rigid entities but probably localized expressions of one fundamental disturbance.

The article is illustrated. W. ZENTMAYER.

VITAMIN "B" COMPLEX DEFICIENCY AS A CAUSE OF RETROBULBAR NEURITIS AND PERIPHERAL NEURITIS IN A CHRONIC ALCOHOLIC AND PIPE SMOKER. B. GOTTLIEB, Brit. J. Ophth. **25:** 556 (Dec.) 1941.

The author supplies the following summary of his article:

"(1) A case of retrobulbar neuritis and peripheral neuritis is described in a chronic alcoholic and pipe smoker.

"(2) Tobacco was of little or no importance in the aetiology.

"(3) The literature is reviewed describing retrobulbar neuritis as occurring in association with other evidences of vitamin B complex deficiency.

"(4) Alcoholic retrobulbar neuritis is considered to be due to vitamin B complex deficiency, probably vitamin B_1.

"(5) Retrobulbar neuritis in pregnancy and some cases of retrobulbar neuritis in diabetes are probably due to vitamin B_1 deficiency.

"(6) Vitamin B complex deficiency, probably vitamin B_1, was the cause of the retrobulbar neuritis and peripheral neuritis in the case described.

"(7) It is suggested that all cases of bilateral retrobulbar neuritis should be investigated as regards the vitamin B content in the diet, particularly if associated with evidences of pellagra, beriberi or peripheral neuritis, and treated accordingly." W. ZENTMAYER.

OCULAR COMPLICATIONS IN HYPEREMESIS GRAVIDARUM. A. J. BALLANTYNE, J. Obst. & Gynaec. Brit. Emp. **48:** 206 (April) 1941.

The ocular signs that accompany pernicious vomiting in the early months of pregnancy have always been put down as retinal hemorrhages of either neurotic or toxic origin. The author has carefully investigated the literature on the etiologic factors, ocular complications, pathologic changes and treatment of pernicious vomiting and gives a report of 6 cases.

He concludes that the description of the ocular changes as retinal hemorrhages, hemorrhagic retinitis or toxic retinitis is incomplete and misleading. A striking feature is that the ocular complications usually start with a defect in the central vision which must be due to optic neuritis, and in the final stage well defined papilledema with flame-shaped hemorrhages radiating from the disk are present, without exudates and without any changes in the blood vessels. Because of the profound loss of vision, the ocular signs differ completely from those of diabetes, nephritis or hypertension. The importance of the condition is that if the diagnosis is not made until the retinal hemorrhages have occurred the pregnancy will have to be terminated and the benefit of an operation may be problematic. It is therefore important that the eye be examined as soon as there is any complaint of loss of vision. Prompt examination usually leads to the correct diagnosis, retrobulbar neuritis. An early correct diagnosis may lead to prompt treatment, in which the intensive use of vitamins B_1 and C play an important part.

The ocular complications begin as retrobulbar optic neuritis, with a central defect in the field and without visible ophthalmoscopic changes. Edema of the papilla and the characteristic peripapillary retinal hemorrhages follow. The condition may lead to total or almost total blindness, which, however, is capable of recovery.

If the persistent vomiting in pregnancy does not respond rapidly and the ocular changes described are present, a prompt termination of the pregnancy is called for, though it is well to remember that the retinal hemorrhages in optic neuritis are late changes and that the ocular involvement should be recognized before they appear. ARNOLD KNAPP.

Therapeutics

SULFANILAMIDE IN THE TREATMENT OF SOME INFECTIONS OF THE EYE. V. CHETVERIKOVA, Vestnik oftal. **18:** 174, 1941.

Sulfanilamide was administered to 85 patients with various coccic infections of the eye. Most of the patients were hospitalized, and they were divided into three groups. The 35 patients in the first group were treated with drops of an aqueous solution of sulfanilamide applied locally. In 25 patients with coniunctival infection. infection of the lids

or corneal ulcer the effect of the treatment was positive. For 18 of these patients bacteriologic examination after treatment gave negative results. The second group consisted of 23 patients to whom sulfanilamide was administered locally (drops or powder to the ulcerated surface) and orally. In 16 (6 with phlegmon of the lacrimal sac, 6 with corneal ulcer and 4 with endophthalmitis) the results of the treatment were good. In the third group, of 27 patients, sulfanilamide was given only orally. The treatment gave positive results in 2 patients with severe pneumococcic conjunctivitis, in 2 with iridocyclitis following cataract extraction and in 13 with phlegmonous inflammation of the lid, orbit and lacrimal sac. Thus the results of treatment were positive in conjunctivitis (as the pneumococci disappeared rapidly) and in phlegmonous inflammation of the sac. Bacteriologic examination of 63 patients showed that 40 harbored pneumococci, 6 streptococci and 10 staphylococci. Thus sulfanilamide is bactericidal for all these cocci, and local application of the drug is indicated in the treatment of external diseases of the eye, while in the diseases of the deeper tissues it should be combined with oral treatment.

A detailed review of the literature is given. O. SITCHEVSKA.

Society Transactions

EDITED BY DR. W. L. BENEDICT

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

KAUFMAN SCHLIVEK, M.D., *Chairman*

BRITTAIN PAYNE, M.D., *Secretary*

November 17, 1941

Tuberous Sclerosis: Clinical Diagnosis in the Case of a 5 Month Old Infant. DR. ISADORE GIVNER.

The purpose of presenting this case of tuberous sclerosis is to emphasize the importance of ophthalmoscopic examination of all infants with epileptiform seizures. The child is the youngest living patient on record for whom a diagnosis of tuberous sclerosis has been made. In addition, the roentgenograms taken after the encephalogram, a means not universally utilized in the study of this disease, confirmed the diagnosis.

The 5 month old infant was first seen on Dec. 26, 1939 at the New York Post-Graduate Medical School and Hospital. The mother stated that for the past month the child had had from three to five convulsions a day. During these attacks the arms and legs were flexed, the hands were clenched, the toes were curled downward, the neck was flexed and the eyes were turned upward and to the right. Three days post partum the mother noticed a convulsion which her physician thought was due to a cerebral hemorrhage. The child was given three blood transfusions and medication containing calcium. The general examination revealed no abnormalities. The report of the neurologic examination was as follows: "There is no paralysis in the arms or legs, no Kernig sign and no apparent asymmetry of the skull, the biceps muscle, the triceps muscle or the achilles tendon. The abdominal reflexes cannot be elicited. Patellar reflexes are equal and active." The spinal fluid was under normal pressure. All laboratory tests gave normal results.

The ophthalmoscopic examination disclosed that in the right eye an area, slightly larger than the disk, midway between the papilla and the macula had the appearance of sharply defined localized edema. There was no evidence of increased intracranial pressure. In the left eye the upper third of the disk and an area extending 2 disk diameters superiorly showed edema similar to that in the right eye. It was elevated to the extent of 5 D. The retinal vessels could be seen through this area.

A diagnosis was made of tuberous sclerosis with retinal phakomatoses. The patient was examined again on Feb. 20, 1940, at which time the right fundus appeared unchanged but the left seemed to be less edematous and contained an oval, dense, white opacity in the nasal portion of the lesion. Typical so-called candle droppings in the ventricle were seen on the encephalogram, which confirmed the diagnosis.

The child was seen again when he was about 27 months old. He was having daily convulsions lasting fifteen minutes; he seldom cried, and if he did he vomited; he weighed 35 pounds (16 Kg.); he did not walk unless held; he did not talk or notice his surroundings, and he had no sense of balance and frequently fell head first.

The appearance of the fundi had changed. An additional lesion had developed in the right eye just below the original one. In the left eye the edema above the disk involved the macula.

DISCUSSION

DR. FERDINAND L. P. KOCH: Bearing in mind Bourneville's original dictum, in 1881, to the effect that tuberous sclerosis probably never would be diagnosed clinically, one should congratulate Dr. Givner on discovering this entity in a living infant only 5 months old.

It is of particular interest that this disease should be recognized prior to the onset of puberty. Since the majority of the cases reported have come to clinical attention during this period, it has been thought that the hormonal changes associated with the appearance of secondary sex characteristics might be responsible in some fashion for the development of the various lesions associated with the syndrome. Unsuccessful efforts have been made by recent investigators to demonstrate clinical carcinogenic constituents in the blood of the patients. The fact that the lesions occur in young children, as observed by other authorities and as reported by Dr. Givner, indicates of course that they are not necessarily dependent on the chemical changes associated with puberty.

With regard to Dr. Givner's case, it is of interest to note that the diagnosis was made by the use of the ophthalmoscope. I agree with Van der Hoeve that not only do all persons in whom the typical retinal tumors are present either have or acquire tuberous sclerosis to some degree but all persons in whom tuberous sclerosis has been discovered by other means (usually at autopsy) also would have been found to have the retinal tumors if an adequate and thorough ophthalmoscopic examination had been carried out.

In four fifths of the cases reported to date the intraocular tumors incident to tuberous sclerosis have been located in the retinas. In the remaining one fifth the tumors have been situated on the disks. Only rarely have they been found to be in juxtaposition with retinal vessels. Additional or secondary smaller tumors have been observed from time to time, and as a rule these have been situated inferiorly to one or more larger tumors. Van der Hoeve stated the belief that these secondary tumors probably could be considered locally implanted metastases. He described the tumors as having the appearance of unripe mulberries although this appearance occasionally was not observed when a tumor on the optic disk was obscured because of papilledema associated with increased intracranial pressure secondary to continued growth of the intracranial tumors.

In this connection I should like to refer to Dr. Algernon B. Reese's observations which he reported before this section two years ago. He mentioned that occasionally subclinical degrees of tuberous sclerosis are overlooked and that the lesions are considered drusen or colloid bodies of the disk. Recently Dr. Reese and I each have had an opportunity to

observe a patient whose disease we thought should be classified in this category. We are not yet prepared to state definitely whether such subclinical varieties of tuberous sclerosis, if they do exist, become more obvious clinically at a later date.

Dr. Givner mentioned both Globus' and Bielschowsky's views concerning the etiology of this disease of nerve tissue about which so little is known. Grinker's opinion also should be mentioned. He stated the belief that the cellular characteristics of the retinal tumors and of the nodules found in the brain are essentially similar; that is, they appear to be of astroblastic origin. Ida Mann, who examined sections of the specimen obtained by Messinger and Clarke, expressed the opinion that the cells of the retinal tumors were glial in origin, probably having been derived from glial cells of the inner neuroblastic layer during the second stage of retinal differentiation, which takes place from the sixth week to the third month of intrauterine development. In this connection, when discussing Dr. Reese's paper two years ago Dr. Tarlau stated that he and Dr. McGrath had been able to verify Grinker's impression that the retinal tumors essentially are astroblastoma and that in the specimens presented by Dr. Reese there existed a striking morphologic resemblance between the astroblasts and the drusen bodies of the disk.

In the drawings of the fundi which Dr. Givner showed, the lesions appeared to be similar to those occurring in the course of protozoan infections, chiefly of the central nervous system, in cases which Dr. Abner Wolf, other physicians and I recently have observed at the Columbia-Presbyterian Medical Center and which comprise a small series of unreported cases. The infecting organism is the protozoan parasite Toxoplasma hominis. The disease develops during late intrauterine life and apparently does not affect the mother. Its initial course is acute, but it tends to become chronic for some months after birth, remaining so until recovery or death occurs. In the early stages the disease resembles low grade generalized encephalomyelitis, and it is manifested in the eyegrounds by bilateral, diffuse, edematous, central chorioretinitis, although similar lesions may appear elsewhere in the fundi. Ophthalmoscopically, deposition of pigment together with chorioretinal atrophy ultimately ensues, and there is marked diminution in or loss of central visual acuity. In our cases at the Medical Center we have never observed a lesion that has the appearance of an unripe mulberry, which is so characteristic of lesions seen in association with tuberous sclerosis.

Later accompanying features of this protozoan infection are: (1) epileptiform seizures of varying degrees, (2) the presence of irregularly distributed small calcified plaques in the brain substance, (3) mental retardation, (4) a positive reaction to immune serologic bodies and (5) the presence of specific parasitic organisms proved at autopsy. The cutaneous lesions usually associated with tuberous sclerosis were never observed in our series of cases, nor was there elicited a history of hereditary or familial diseases of a similar nature.

Therefore, with the exception of convulsions and mental retardation, the essential features of toxoplasmosis are not the same as those of tuberous sclerosis. However, tuberous sclerosis in a 5 month old infant might present variations differing from the disease as observed in older patients. It is difficult, for example, to correlate the encephalographic

findings in Dr. Givner's case with an entity other than tuberous sclerosis. It would be of interest to obtain also an electroencephalographic tracing as well as to determine the presence or absence of immune serologic bodies. The information obtained would be of positive value in making the differential diagnosis.

DR. ISADORE GIVNER: I am not familiar with the pathologic changes present in the eye in cases of toxoplasmosis. However, it would seem unlikely that in such an infective process the spinal fluid would be clear and its cell count within normal limits, as in tuberous sclerosis.

The encephalogram in this case revealed typical so-called candle droppings in the ventricle. It was reviewed by competent radiologists, who were unanimous concerning the diagnosis of tuberous sclerosis.

Dr. Koch mentioned deposition of pigment together with chorioretinal atrophy occurring in some cases which he has observed. As to the case that I have reported, the child has been observed for two years, during which time the edema of the left fundus has receded. There has been no pigmentary disturbance at any time. Some calcified areas are appearing in the masses. These possibly may develop into more solid forms, such as are usually present in cases of tuberous sclerosis, if the patient lives long enough.

Subsequent studies, including tests for toxoplasmotic immune reactions of the blood and the spinal fluid, have definitely ruled out encephalomyelitis due to Toxoplasma and have confirmed the diagnosis of tuberous sclerosis.

Lymphosarcoma of the Lacrimal Gland. DR. CHARLES A. PERERA.

This article will be published in full in a later issue of the ARCHIVES.

Actinomycosis of Conjunctiva Associated with Superficial Punctate Keratitis. DR. GORDON BRUCE.

This case was reported in detail in an article by Dr. Gordon Bruce and Dr. Devorah Locatcher-Khorazo (Actinomyces: Recovery of the Streptothrix in a Case of Superficial Punctate Keratitis, ARCH. OPHTH. **27:** 294 [Feb.] 1942).

DISCUSSION

DR. JAMES GARFIELD DWYER: No doubt many patients with actinomycosis are being treated in whom the disease is not recognized. It is prevalent throughout North America and especially so in the state of New York and in Canada. In 1937 the late Dr. Gay wrote a tremendous volume concerning all the obscure, unknown and little known infections, and in it are many pages pertaining to actinomycotic infection occurring in various parts of the body. It is a common disease. If the lesion is superficial it is easily recognized, but if it is deep seated there may be difficulty in making a diagnosis. The first impression may be that the lesion is tuberculous. A 9 per cent solution of salt agar is the special medium used to isolate the organism. It will prevent the growth of staphylococci or streptococci but not the growth of the mold. It is interesting to note that actinomycosis is now placed in the same classification as tuberculosis. Conjunctivitis in many cases is being treated in the same manner as infections of bacterial origin, whereas conjunctivitis is

really an infection due to mold. Actinomycosis of the nose and mouth is common. There are cases on record in which a tooth was extracted and Actinomyces observed on culture. Libman said that actinomycosis is common in England, where it is called "manure disease of the eye" because it is spread by dried manure. Careful bacteriologic investigation is necessary to isolate the mold.

The Vollmer Tuberculin Patch Test: Its Possibilities in Ophthalmic Practice. DR. BENJAMIN FRIEDMAN and DR. FRANK KEIL JR. (by invitation):

This article was published in full in the April issue of the ARCHIVES, page 728.

DISCUSSION

DR. BENJAMIN FRIEDMAN: We should like to emphasize that our report is simply a comparison between special applications of the percutaneous and the intracutaneous method of making tuberculin tests.

The diagnosis of ocular tuberculosis is exceedingly difficult to establish because the bacillus is almost never obtained from the lesion and because the reaction to tuberculin may have been positive long before the ocular disease developed. If a patient who has a positive Wassermann reaction has a lesion in his eye later on the question as to whether the lesion is syphilitic may be decided by the occurrence or nonoccurrence of prompt improvement with antisyphilitic treatment. But in ocular tuberculosis there is no such therapeutic test, because tuberculosis responds little if at all to specific therapy. Furthermore, the Mantoux reaction is positive in cases of tuberculosis of the eye much less frequently than in cases of tuberculosis of the lungs, glands, skin and bones. A diagnosis of ocular tuberculosis by the exclusion of other etiologic probabilites is made only by inference.

The patients included in our series were at most suspected of having tuberculosis; in no case was the diagnosis of tuberculosis proved. It might be best, therefore, to consider our report as being based on reactions to tuberculin in patients with mixed ocular lesions; indeed, we might have chosen an equal number of healthy adults and probably have had no greatly different responses.

The only question we wished to solve was whether the Vollmer test is as informative as the Mantoux test in revealing positive reactions among patients encountered in everyday clinical practice.

There is no doubt that for children the patch test will replace the preliminary intracutaneous test. From children one may expect accurate responses to the patch test. As for adults, it may be necessary to supplement the patch test with the Mantoux test in a certain number of instances, but even if only 75 per cent of the patch test were efficacious, the necessity of performing three fourths of the initial Mantoux tests would be eliminated.

Preliminary tests may sensitize a few persons to tuberculin; a repetition of the same dose after a negative reaction may ocasionally yield a positive reaction. A stronger second dose has a double advantage; the sensitivity of the patient as well as the concentration of tuberculin may be increased. The stronger second dose is more likely to produce a posi-

tive reaction than the preliminary dose. It is conceivable that a certain number of positive second reactions are in reality "false positive" reactions.

We realize that our series of adult patients who react to the patch test is small, and we should like to ask physicians who are interested to repeat these studies in order that a firmer statistical evaluation of the patch test may be obtained. It might be preferable to assay the Vollmer test against a test with 0.1 mg. of old tuberculin in order to correlate the results with those of the pediatricians, by whom 0.1 mg. of old tuberculin is used almost universally as a standard.

Mechanism of Formation of Intraocular Fluids. DR. JONAS S. FRIEDENWALD (by invitation): Baltimore.

This article will be published in full in a later issue of the ARCHIVES.

Book Reviews

Consideraciones anátomoclínicas sobre la vía óptica retroquiasmática. By Jorge Balbrán, M.D. Pp. 130, with numerous illustrations in black and in color. Buenos Aires: El Ateneo, 1941.

This excellent monograph deals with the anatomy of the optic tract and the clinical symptoms of its lesions. The author starts with an anatomic description of the retrochiasmatic path as he has found it by his own researches and his clinical work. He believes that of the two end branches of the tract, internal and external, only the external, which goes to the geniculate body, forms part of the optic pathway. All nerve fibers which transmit visual sensations end at the external geniculate body. The internal branch of the tract has nothing to do with the optic pathway.

Each tract contains (1) direct, or temporal, peripheral fibers; (2) direct, or temporal, macular fibers, superior and inferior; (3) crossed, or nasal, peripheral fibers, superior and inferior, and (4) crossed, or nasal, macular fibers, superior and inferior. When they reach the external geniculate body these fibers can be followed to the limit between the anterior fourth and the posterior three fourths of the lower surface of the geniculate body.

The external geniculate body is described with excellent schematic and microscopic pictures of its different layers and fiber junctions.

A study of the course of the "optic radiation" from the external geniculate body to the inferior longitudinal pathway following the work of Balado and Franke is presented.

The author then considers the cortical center of vision in the occipital lobe. He traces the history of the striated area from Gennari and Vicq d'Azyr to the present time and considers the different layers of the striated cortex, comparing them with the rest of the occipital cortex.

In the second chapter Malbrán deals with the clinical symptoms of diseases of the tract and supports, with campimetric charts and clinical histories, the opinion that macular fibers occupy a central position in the tract, that the dorsal fibers are connected with the upper part of the retina and that the ventral fibers correspond to the lower part of the retina. Macular vision may or may not be spared in the hemianopias caused by lesions of the tracts.

In the third chapter he reports on a case of primitive involvement of the external geniculate body, a rare occurrence. He asserts that partial lesions of this body produce homonymous incongruent hemianopia and that the macular fibers end in the anterior portion of the geniculate body.

In the last two chapters the author deals with pathologic processes affecting the optic radiation. From his clinical findings he concludes that the nerve fibers which correspond to the superior half of the retina and to the macula end in the optic radiation. He asserts that the so-called loop of Meyer does not exist.

The colored charts showing the pathway of the fibers from the nerve to the occipital lobe are illuminating.

Balado and the author attribute to the macula an extensive representation in the cortical center of vision.

M. Uribe Troncoso.

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INTERNATIONAL

International Association for Prevention of Blindness

President: Dr. P. Bailliart, 66 Boulevard Saint-Michel, Paris, 6e, France.
Secretary-General: Prof. M. Van Duyse, Université de Gand, Gand, Prov. Ostflandern, Belgium.
All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6e, France.

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Secretary: Dr. Ehlers, Jerbanenegade 41, Copenhagen, Denmark.

International Organization Against Trachoma

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Pan-American Congress of Ophthalmology

President: Dr. Harry S. Gradle, 58 E. Washington St., Chicago.
Executive Secretaries: Dr. Conrad Berens, 35 E. 70th St., New York. Dr. M. E. Alvaro, 1511 Consolacao, São Paulo, Brazil.

FOREIGN

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Secretary: Dr. Frederick Ridley, 12 Wimpole St., London, W. 1.

Chinese Ophthalmology Society

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Secretary: Dr. F. S. Tsang, 221 Foochow Rd., Shanghai.

Chinese Ophthalmological Society of Peiping

President: Dr. H. T. Pi, Peiping Union Medical College, Peiping.
Secretary: Dr. C. K. Lin, 180 Hsi-Lo-yen, Chienmeng, Peiping.
Place: Peiping Union Medical College, Peiping. Time: Last Friday of each month.

German Ophthalmological Society

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Secretary: Prof. E. Engelking, Heidelberg.

Hungarian Ophthalmological Society

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Assistant Secretary: Dr. Stephen de Grósz, University Eye Hospital, Mária-utca 39, Budapest.
All correspondence should be addressed to the Assistant Secretary.

Midland Ophthalmological Society

President: Dr. W. Niccol, 4 College Green, Gloucester, England.
Secretary: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Place: Birmingham and Midland Eye Hospital.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

NORTH OF ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. A. MacRae, 6 Jesmond Rd., Newcastle-upon-Tyne, England.
Secretary: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Place: Manchester, Bradford, Leeds, Newcastle-upon-Tyne, Liverpool and Sheffield, in rotation. Time: October to April.

OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA

President: Dr. A. James Flynn, 135 Macquarie St., Sydney.
Secretary: Dr. D. Williams, 193 Macquarie St., Sydney.

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Secretary: Dr. Mohammed Khalil, 4 Baehler St., Cairo.
All correspondence should be addressed to the secretary, Dr. Mohammed Khalil.

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

President: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Secretary: Mr. L. H. Savin, 7 Queen St., London, W. 1, England.

OPHTHALMOLOGY SOCIETY OF BOMBAY

President: Dr. D. D. Sathaye, 127 Girgaum Rd., Bombay 4, India.
Secretary: Dr. H. D. Dastur, Dadar, Bombay 14, India.
Place: H. B. A. Free Ophthalmic Hospital, Parel, Bombay 12. Time: First Friday of every month.

OXFORD OPHTHALMOLOGICAL CONGRESS

Master: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.

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Place: Lindley'a 4, Warsaw.

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SOCIEDAD OFTALMOLOGIA DEL LITORAL, ROSARIO (ARGENTINA)

President: Prof. Dr. Carlos Weskamp, Laprida 1159, Rosario.
Secretary: Dr. Juan M. Vila Ortiz, Córdoba 1433, Rosario.
Place: Rosario. Time: Last Saturday of every month, April to November, inclusive.
All correspondence should be addressed to the President.

SOCIEDADE DE OPHTHALMOLOGIA E OTO RHINO-LARYNGOLOGIA DA BAHIA

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Secretary: Dr. Adroaldo de Alencar, Brazil.
All correspondence should be addressed to the President.

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Secretary: Dr. Sadger Max, 9 Bialik St., Tel Aviv, Palestine.

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Chairman: Dr. Lawrence T. Post, 508 N. Grand Blvd., St. Louis, Mo.
Secretary: Dr. Derrick Vail, 441 Vine St., Cincinnati.
Place: Atlantic City. Time: June 8-12, 1942.

American Academy of Ophthalmology and Otolaryngology, Section on Ophthalmology

President: Dr. Ralph I. Lloyd, 14–8th Ave., Brooklyn.
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Executive Secretary-Treasurer: Dr. William P. Wherry, 1500 Medical Arts Bldg., Omaha.

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Association for Research in Ophthalmology, Inc.

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President: Dr. Alexander E. MacDonald, 170 St. George St., Toronto.
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Canadian Ophthalmological Society

President: Dr. J. Vaillancourt, 46 St. Louis St., Quebec.
Secretary-Treasurer: Dr. Alexander E. MacDonald, 421 Medical Arts Bldg., Toronto.

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President: Mr. Mason H. Bigelow, 1790 Broadway, New York.
Secretary: Miss Regina E. Schneider, 1790 Broadway, New York.
Executive Director: Mrs. Eleanor Brown Merrill, 1790 Broadway, New York.

SECTIONAL

Academy of Medicine of Northern New Jersey, Section on Eye, Ear, Nose and Throat

President: Dr. Charles W. Barkhorn, 223 Roseville Ave., Newark.
Secretary: Dr. William F. McKim, 317 Roseville Ave., Newark.
Place: 91 Lincoln Park South, Newark. Time: 8:45 p. m., second Monday of each month, October to May.

Central Wisconsin Society of Ophthalmology and Otolaryngology

President: Dr. D. G. Hugo, 130 Main St., Oshkosh.
Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.
Time: October 1942.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. William D. Rowland, 84 Commonwealth Ave., Boston.
Secretary-Treasurer: Dr. Trygve Gundersen, 243 Charles St., Boston.
Place: Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston. Time: 8 p. m., third Tuesday of each month from November to April, inclusive.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President: Dr. Ralph A. Fenton, 1020 S. W. Taylor St., Portland, Ore.
Secretary-Treasurer: Dr. C. Allen Dickey, 450 Sutter St., San Francisco.
Place: Portland, Ore. Time: May 11-14, 1942.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Spencer S. Howe, 103 E. Holly St., Bellingham, Wash.
Secretary-Treasurer: Dr. Barton E. Peden, 419 Stimson Bldg., Seattle.
Place: Seattle or Tacoma, Wash. Time: Third Tuesday of each month, except June, July and August.

ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. J. Sheldon Clark, 27 E. Stephenson St., Freeport, Ill.
Secretary-Treasurer: Dr. Harry R. Warner, 321 W. State St., Rockford, Ill.
Place: Rockford, Ill., or Janesville or Beloit, Wis. Time: Third Tuesday of each month from October to April, inclusive.

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Secretary-Treasurer: Dr. J. H. Curts, 330 S. Washington Ave., Saginaw, Mich.
Place: Saginaw or Bay City, Mich. Time: Second Tuesday of each month, except July and August.

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Secretary-Treasurer: Dr. J. E. Dvorak, 408 Davidson Bldg., Sioux Falls, S. D.

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Secretary: Dr. J. W. Jervey Jr., 101 Church St., Greenville, S. C.
Place: Richmond, Va. Time: November 1942.

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Secretary: Dr. A. E. Cruthirds, 1011 Professional Bldg., Phoenix, Ariz.
Place: Albuquerque, N. Mex. Time: November 1942.

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President: Dr. W. M. Dodge, 716 First National Bank Bldg., Battle Creek.
Secretary-Treasurer: Dr. Kenneth Lowe, 25 W. Michigan Ave., Battle Creek.
Time: Last Thursday of September, October, November, March, April and May.

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

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Secretary-Treasurer: Dr. J. McClure Tyson, Deposit Nat'l Bank Bldg., DuBois.

STATE

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Secretary-Treasurer: Dr. Raymond C. Cook, 701 Main St., Little Rock.

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President: Dr. William M. Bane, 1612 Tremont Pl., Denver.
Secretary: Dr. Harry Shankel, Republic Bldg., Denver.
Place: University Club, Denver. Time: 7:30 p. m., third Saturday of each month, October to May, inclusive.

Connecticut State Medical Society, Section on Eye, Ear, Nose and Throat

President: Dr. Edward N. DeWitt, 836 Myrtle Ave., Bridgeport.
Secretary-Treasurer: Dr. Henry L. Birge, 179 Allyn St., Hartford.

Eye, Ear, Nose and Throat Club of Georgia

President: Dr. E. N. Maner, 247 Bull St., Savannah.
Secretary-Treasurer: Dr. C. K. McLaughlin, 567 Walnut St., Macon.

Indiana Academy of Ophthalmology and Oto-Laryngology

President: Dr. F. McK. Ruby, Union City.
Secretary: Dr. Edwin W. Dyar Jr., 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

Iowa Academy of Ophthalmology and Oto-Laryngology

President: Dr. J. K. Von Lackum, 117–3d St. S. E., Cedar Rapids.
Secretary-Treasurer: Dr. B. M. Merkel, 604 Locust St., Des Moines.

Louisiana-Mississippi Ophthalmological and Otolaryngological Society

President: Dr. Henry N. Blum, 912 American Bank Bldg., New Orleans.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

Michigan State Medical Society, Section of Ophthalmology and Otolaryngology

Chairman: Dr. Robert H. Fraser, 25 W. Michigan Ave., Battle Creek.
Secretary: Dr. R. G. Laird, 114 Fulton St., Grand Rapids.

Minnesota Academy of Ophthalmoloy and Otolaryngology

President: Dr. Erling Wilhelm Hansen, 78 S. 9th St., Minneapolis.
Secretary-Treasurer: Dr. George E. McGeary, 920 Medical Arts Bldg., Minneapolis.
Time: Second Friday of each month from October to May.

Montana Academy of Oto-Ophthalmology

President: Dr. William J. Marshall, 335 Owen St., Missoula.
Secretary: Dr. Fritz D. Hurd, 309 Medical Arts Bldg., Great Falls.

Nebraska Academy of Ophthalmology and Otolaryngology

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

New Jersey State Medical Society, Section on Ophthalmology, Otology and Rhinolaryngology

Chairman: Dr. Edgar P. Cardwell, 47 Central Ave., Newark.
Secretary: Dr. Arthur E. Sherman, 243 S. Harrison St., East Orange.

New York State Medical Society, Eye, Ear, Nose and Throat Section

Chairman: Dr. Searle B. Marlow, 109 S. Warren St., Syracuse.
Secretary: Dr. C. Stewart Nash, 277 Alexander St., Rochester.

North Carolina Eye, Ear, Nose and Throat Society

President: Dr. M. R. Gibson, Professional Bldg., Raleigh.
Secretary: Dr. Vanderbilt F. Couch, 105 W. 4th St., Winston-Salem.

North Dakota Academy of Ophthalmology and Oto-Laryngology

President: Dr. G. A. Larson, 114 Roberts St., Fargo.
Secretary-Treasurer: Dr. F. L. Wicks, 516–6th St., Valley City.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Paul Bailey, 833 S. W. 11th Ave., Portland.
Secretary-Treasurer: Dr. R. S. Fixott, 1020 S. W. Taylor St., Portland.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. J. L. Sanders, 222 N. Main St., Greenville.
Secretary: Dr. J. H. Stokes, 125 W. Cheves St., Florence.
Place: Columbia. Time: November 1942.

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Wesley Wilkerson, 700 Church St., Nashville.
Secretary-Treasurer: Dr. W. D. Stinson, 124 Physicians and Surgeons Bldg., Memphis.

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. E. L. Goar, 1300 Walker Ave., Houston.
Secretary: Dr. Dan Brannin, 929 Medical Arts Bldg., Dallas.

UTAH OPHTHALMOLOGICAL SOCIETY

President: Dr. Everett B. Muir, Boston Bldg., Salt Lake City.
Secretary-Treasurer: Dr. Earl H. Phillips, 623 Judge Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President: Dr. Mortimer H. Williams, 30½ Franklin Rd. S. W., Roanoke.
Secretary-Treasurer: Dr. Meade Edmunds, 34 Franklin St., Petersburg.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. George E. Ferguson, Second National Bldg., Akron, Ohio.
Secretary-Treasurer: Dr. D. F. Mathias, First Central Tower, Akron, Ohio.
Time: First Monday in January, March, May and November.

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Stacy C. Howell, 144 Ponce de Leon Ave. N. E., Atlanta, Ga.
Secretary: Dr. Lester A. Brown, 478 Peachtree St. N. E., Atlanta, Ga.
Place: Grady Hospital. Time: 6:00 p. m., second Wednesday of each month, from October to May.

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Ernst Bodenheimer, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Thomas R. O'Rourk, 104 W. Madison St., Baltimore.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m., fourth Thursday of each month from October to March.

Birmingham Eye, Ear, Nose and Throat Club

President: Each member, in alphabetical order.
Secretary: Dr. Luther E. Wilson, 919 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. Maurice Wieselthier, 1322 Union St., Brooklyn.
Secretary-Treasurer: Dr. Harold F. Schilback, 142 Joralemon St., Brooklyn.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. Meyer H. Riwchun, 367 Linwood Ave., Buffalo.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo.
Time: Second Thursday of each month.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Chattanooga Bank Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. Sanford Gifford, 720 N. Michigan Ave., Chicago.
Secretary-Treasurer: Dr. Vernon M. Leech, 55 E. Washington St., Chicago.
Place: Chicago Towers Club, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati General Hospital Ophthalmology Staff

Chairman: Dr. D. T. Vail, 441 Vine St., Cincinnati.
Secretary: Dr. A. A. Levin, 441 Vine St., Cincinnati.
Place: Cincinnati General Hospital. Time: 7:45 p. m., third Friday of each month except June, July and August.

Cleveland Ophthalmological Club

Chairman: Dr. W. J. Abbott, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. L. V. Johnson, 2065 Adelbert Rd., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. Francis H. Adler, 313 S. 17th St., Philadelphia.
Clerk: Dr. W. S. Reese, 1901 Walnut St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. C. D. Postle, 240 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. Hugh C. Thompson, 289 E. State St., Columbus, Ohio
Place: The Neil House. Time: 6 p. m., first Monday of each month.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. F. K. Stroud, 416 Chaparral St., Corpus Christi, Texas.
Secretary: Dr. Arthur Padilla, 414 Medical Professional Bldg., Corpus Christi, Texas.
Time: Second Friday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. L. A. Nelson, 4105 Live Oak St., Dallas, Texas.
Secretary: Dr. S. F. Harrington, 921 Medical Arts Bldg., Dallas, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. C. Schmitz, 604 Locust St., Des Moines, Iowa.
Secretary-Treasurer: Dr. Byron M. Merkel, 604 Locust St., Des Moines, Iowa.
Time: 7:45 p. m., third Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Members rotate alphabetically.
Secretary: Dr. Harvey E. Dowling, 2414 Eaton Tower, Detroit.
Time: 6:30 p. m., first Wednesday of each month.

Detroit Ophthalmological Society

President: Dr. Parker Heath, 1553 Woodward Ave., Detroit.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Place: Club rooms of Wayne County Medical Society. Time: Third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Dr. James M. Dunn, 1352 Union St., Schenectady.
Secretary-Treasurer: Dr. Joseph L. Holohan, 330 State St., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Eastern Pennsylvania Association of Eye, Ear, Nose and Throat Physicians

President: Dr. James E. Landis, 232 N. 6th St., Reading.
Secretary-Treasurer: Dr. Sterling F. Mengel, 612 W. Market St., Pottsville.
Time: Last week in April each year.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. W. R. Thompson, 602 W. 10th St., Fort Worth, Texas.
Secretary-Treasurer: Dr. A. E. Jackson, 602 W. 10th St., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. Felician J. Slataper, 1110-1111 Medical Arts Bldg., Houston, Texas.
Secretary: Dr. Theo. L. Holland, 611 Medical Arts Bldg., Houston, Texas.
Place: Medical Arts Bldg., Harris County Medical Society Rooms. Time: 8 p. m., second Thursday of each month from September to June.

Indianapolis Ophthalmological and Otolaryngological Society

President: Dr. John I. Garret, 57 Stokes Bldg., Indianapolis.
Secretary: Dr. Kenneth L. Craft, 23 E. Ohio St., Indianapolis.
Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

Kansas City Society of Ophthalmology and Oto-Laryngology

President: Dr. Homer Beal, 1103 Grand Ave., Kansas City, Mo.
Secretary: Dr. Desmond Curran, Federal Reserve Bank Bldg., Kansas City, Mo.
Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Long Beach Eye, Ear, Nose and Throat Society

Chairman: Dr. Harold Snow, 614 S. Pacific Ave., San Pedro, Calif.
Secretary-Treasurer: Dr. Oliver R. Nees, 508 Times Bldg., Long Beach, Calif.
Place: Professional Bldg. Time: Last Wednesday of each month from October to May.

Los Angeles Society of Ophthalmology and Otolaryngology

President: Dr. John Osburn, 523 W. 6th St., Los Angeles.
Secretary-Treasurer: Dr. Colby Hall, 1136 W. 6th St., Los Angeles.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:00 p. m., fourth Monday of each month from September to May, inclusive.

Louisville Eye and Ear Society

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.
Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.
Place: Brown Hotel. Time: 6:30 p. m., second Thursday of each month from September to May, inclusive.

Lower Anthracite Eye, Ear, Nose and Throat Society

Chairman: Each member in alphabetical order.
Secretary: Dr. James J. Monohan, 31 S. Jardin St., Shenendoah, Pa.

Medical Society of the District of Columbia, Section of Ophthalmology and Otolaryngology

Chairman: Dr. E. J. Cummings, 1835 I St. N. W., Washington.
Secretary: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.
Place: 1718 M St. N. W. Time: 8 p. m., third Friday of each month from October to April, inclusive.

Memphis Society of Ophthalmology and Otolaryngology

Chairman: Each member, in alphabetical order.
Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.
Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p. m., second Tuesday of each month from September to May.

Milwaukee Oto-Ophthalmic Society

President: Dr. John W. Truitt, 161 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.
Place: University Club. Time: 6:30 p. m., second Tuesday of each month.

Montgomery County Medical Society

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.
Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.
Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. J. Rosenbaum, 1396 Ste. Catherine St. W., Montreal, Canada.
Secretary: Dr. L. Tessier, 1230 St. Joseph Blvd. E., Montreal, Canada.
Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. Andrew Hollabaugh, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Guy Maness, Medical Arts Bldg., Nashville, Tenn.
Place: St. Thomas Hospital. Time: 8 p. m., third Monday of each month from October to May.

New Haven Ophthalmological Society

President: Dr. William H. Ryder, 185 Church St., New Haven, Conn.
Secretary: Dr. Frederick A. Wies, 255 Bradley St., New Haven, Conn.

New Orleans Ophthalmological and Otolaryngological Society

President: Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.
Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.
Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman: Dr. Kaufman Schlivek, 1016–5th Ave., New York.
Secretary: Dr. Brittain Payne, 896 Madison Ave., New York.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

President: Dr. Isidore Givner, 108 E. 66th St., New York.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York.
Place: Squibb Hall, 745–5th Ave. Time: 8 p. m., first Monday of each month from October to May, inclusive.

OKLAHOMA CITY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. R. E. Leatherock, Cushing, Okla.
Secretary: Dr. Harry C. Ford, 1014 Medical Arts Bldg., Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

OMAHA AND COUNCIL BLUFFS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. Leo P. Coakley, 918 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m., dinner; 7 p. m., program; third Wednesday of each month from October to May.

PASSAIC-BERGEN OPHTHALMOLOGICAL CLUB

President: Dr. L. Markowitz, 16 Church St., Paterson, N. J.
Secretary-Treasurer: Dr. A. John Reinhorn, 302 Broadway, Paterson, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

PHILADELPHIA COUNTY MEDICAL SOCIETY, EYE SECTION

Chairman: Dr. Edmund B. Spaeth, 1930 Chestnut St., Philadelphia.
Secretary: Dr. Wilfred E. Fry, 1819 Chestnut St., Philadelphia.
Time: First Thursday of each month from October to May.

PITTSBURGH OPHTHALMOLOGICAL SOCIETY

President: Dr. J. Clyde Markel, 200–9th St., Pittsburgh.
Secretary: Dr. George H. Shuman, 351–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

READING EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Solon L. Rhode, 238 N. 6th St., Reading, Pa.
Secretary: Dr. Paul C. Craig, 232 N. 5th St., Reading, Pa.
Place: Wyomissing Club. Time: 6:30 p. m., third Wednesday of each month from October to July.

RICHMOND OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. W. F. Bryce, Medical Arts Bldg., Richmond, Va.
Secretary: Dr. Richard W. Vaughan, Medical Arts Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

ROCHESTER EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. E. J. Avery, 11 N. Goodman St., Rochester, N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester, N. Y.

St. Louis Ophthalmic Society

President: Dr. William M. James, 508 N. Grand Blvd., St. Louis.
Secretary: Dr. H. Rommel Hildreth, 823 Metropolitan Bldg., St. Louis.
Place: Oscar Johnson Institute. Time: Clinical meeting 5:30 p. m., dinner and scientific meeting 6:30 p. m., fourth Friday of each month from October to April, inclusive, except December.

San Antonio Ophthalmo-Oto-Laryngological Society

President: Dr. Dan Russell, 705 E. Houston St., San Antonio, Texas.
Secretary-Treasurer: Dr. P. G. Bowen, 315 Camden St., San Antonio, Texas.
Place: Bexar County Medical Library. Time: 8 p. m., first Tuesday of each month from October to May.

San Francisco County Medical Society, Section on Eye, Ear, Nose and Throat

Chairman: Dr. Fred Boyle, 490 Post St., San Francisco.
Secretary: Dr. Frank Hand, 450 Sutter St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

Shreveport Eye, Ear, Nose and Throat Society

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

Spokane Academy of Ophthalmology and Oto-Laryngology

President: Dr. Louis A. Parsell, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. Robert L. Pohl, 407 Riverside Ave., Spokane, Wash.
Place: Paulsen Medical and Dental Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

Syracuse Eye, Ear, Nose and Throat Society

President: Dr. Roy Seeley Moore, 1704 State Tower Bldg., Syracuse, N. Y.
Secretary-Treasurer: Dr. I. H. Blaisdell, 713 E. Genesee St., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

Toledo Eye, Ear, Nose and Throat Society

Chairman: Dr. John D. Skow, 2001 Collingwood Blvd., Toledo, Ohio.
Secretary: Dr. S. H. Patterson, 125–15th Ave., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

Toronto Academy of Medicine, Section of Ophthalmology

Chairman: Dr. W. R. F. Luke, 316 Medical Arts Bldg., Toronto, Canada.
Secretary: Dr. W. T. Gratton, 216 Medical Arts Bldg., Toronto, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

Washington, D. C., Ophthalmological Society

President: Dr. E. Leonard Goodman, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. Sterling Bockoven, 1752 Massachusetts Ave. N. W., Washington, D. C.
Place: Episcopal Eye, Ear and Throat Hospital. Time: 7:30 p. m., first Monday in November, January, March and April.

Wilkes-Barre Ophthalmological Society

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.

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